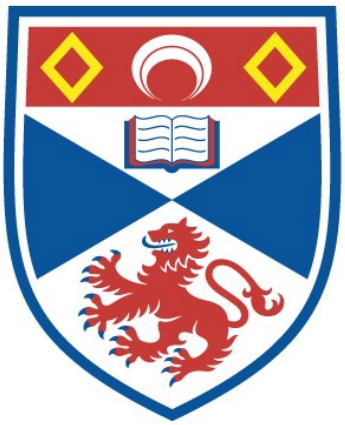
SOME SUBSTITUTION REACTIONS OF ARYLATED AZA-HETEROCYCLES

Khalid Javaid

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1984

SOME SUBSTITUTION REACTIONS

OF ARYLATED AZA-HETEROCYCLES

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presented by

KHALID JAVAID

to the

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in application for

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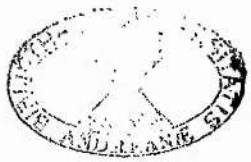
May, 1984



This thesis is dedicated to my parents and wife.

ACKNOWLEDGEMENTS

I sincerely thank Dr. D. M. Smith for his patience, help and encouragement over the past three and a half years. I also thank Professors Lord Tedder and P. A. H. Wyatt for the use of the research facilities in the Department of Chemistry.

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Thanks also go to Dr. M. Aslam Khan, for selecting me for these studies the present Chief Scientist and Scientific Advisor for extension of my stay to complete my work, and the Ministry of Defence for leave of absence and financial support.

I will also like to thank my wife and children for their patience and my brother-in-law Maj. General M. Saeed Khan for looking after my family.

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition and has not previously been presented for a Higher Degree.

This work was carried out in the Department of Chemistry of the University of St. Andrews under the supervision of Dr. D. M. Smith. The work commenced on 14th January, 1981, the date of my joining the University of St. Andrews as a research student.

(Khalid Javaid)

CERTIFICATE

I hereby certify that Khalid Javaid has spent thirteen terms at research work under my supervision, has fulfilled the conditions of the Resolution of the University Court 1967, No. 1 and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

D. M. Smith,

Research Supervisor

COURSES ATTENDED AND QUALIFIED

1. Reaction Mechanism, Unit 1 (Third Year)
2. Heterocyclic Chemistry, Unit 4 (Third Year)
3. Reactive Intermediates, Unit 7 (Second Year)
4. Synthesis, Unit 9 (Third Year)
5. Principles of Organic Synthesis, Unit 12 (Second Year).

Contents

SUMMARY

The nitration of 2,5-diphenyl-1,3,4-thiadiazole is investigated and the results are compared with the nitration results of 2,5-diphenyl-1,3,4-oxadiazole. The variation of isomer ratios with variation in nitration media occurs in the thiadiazole series, but not to the extent it occurs in the oxadiazole series. As the nitrating agent is changed from nitric acid alone to nitric acid in sulphuric acid, and then to nitronium tetrafluoroborate, the proportion of meta-nitrated products increases at the expense of para-nitrated compounds. The significance of these results, and those in other related phenyl heterocycles, are discussed.

The attempted monobromination of 2-phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole is described. Previous attempts always resulted in polybromination of the phenyl ring. We were able to restrict the reaction to dibromination, the first bromine entering the ring in all the three positions in the ratio of ortho:meta:para = 28.5: 28.5: 43. The second bromine entering was ortho or para to the first bromine already present in the phenyl ring.

Synthesis of (1,3,4-oxadiazole-2,5-diyl)dibenzoic acids and thiadiazole analogues of these acids is undertaken by oxidation of the corresponding ditolyl-oxadiazoles and -thiadiazoles. Previously described routes to these acids (some of them patented procedures) did not give satisfactory yields.

Chapter 1

Introduction

The Synthesis of 2,5-Diaryl-1,3,4-oxadiazoles and -thiadiazoles

Stolle[1] and Gunther[2] prepared 2,5-diphenyl-1,3,4-oxadiazole before 1900 and there are several reviews on this subject[3-6]. Investigations in this field have intensified due to the uses of 2,5-diaryl-1,3,4-oxadiazoles in a number of diverse fields such as dyestuffs[7-9], particularly anthraquinone vat dyes and azo-dyes; drugs[10-14] like 2-(hydroxyphenyl)-1,3,4-oxadiazole and sulphonamide derivatives of 1,3,4-oxadiazoles; and colour intensifiers[15,16] like 2-(o-alkoxyphenyl)-1,3,4-oxadiazoles. Consequently patents[17-21] make up a large portion of the recent literature. Uses of various substituted oxadiazoles as monomers for thermally stable polymers[22-24] in the 'fifties have brought many industrial giants like ICI, Du Pont, CIBA and Kodak into this field.

The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazine by Emil Fischer and hydrazine by Th. Curtius in the late nineteenth century. The first 1,3,4-thiadiazole was prepared by Fischer[25] in 1882; development and expansion of 1,3,4-thiadiazole chemistry in the early part of the twentieth century owes much to the work of Busch and his coworkers[26].

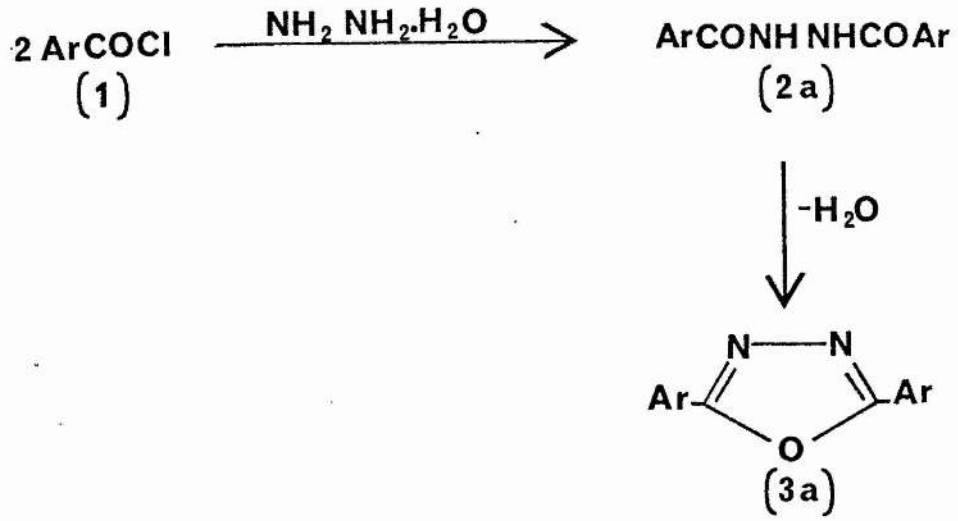
The work slowed down during and between the two World Wars but the discovery of sulpha-drugs[27], such as 2-acetamido-1,3,4-thiadiazole- 5-sulphonamide and subsequent use of di-substituted 1,3,4-thiadiazoles as monomers [e.g. (1,3,4-thiadiazole-2,5-diyl)dibenzoic acid for the manufacture of synthetic fibre], renewed the interest in the development and manufacture of these and other related compounds. The pharmaceutical[28-32], dyestuff[32], and fibre[22-24,33] interests have continued resulting in the discovery of many more interesting compounds and procedures.

1.2 Synthesis

2,5-Diaryl-1,3,4-oxadiazoles are generally prepared by cyclisation with elimination of water from diaroylhydrazines with a suitable dehydrating agent.

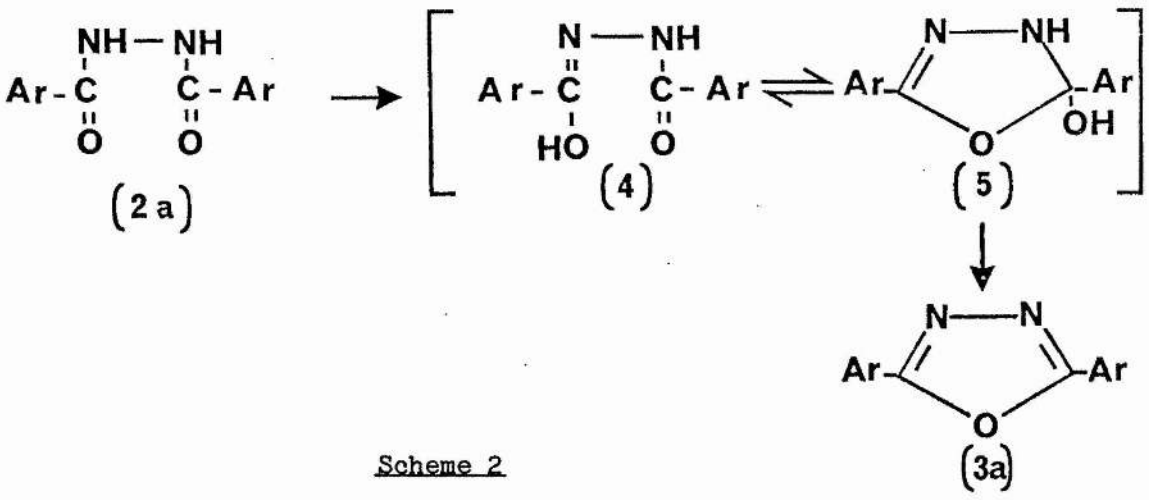
Symmetrical diaroylhydrazines are usually prepared by reacting 2 mole equivalents of an aroyl chloride (1) with one mole equivalent of hydrazine hydrate in dry pyridine[34]. An alternative method uses anhydrous sodium carbonate as the base in N,N-dimethylacetamide[35] or N,N-dimethylformamide. This method was generally applied for our preparations.

One method of preparing a 2,5-diaryl-1,3,4-oxadiazole (3a) is by heating a diaroylhydrazine (2a) with phosphorus oxychloride till it dissolves completely (Scheme 1)[34,35] .



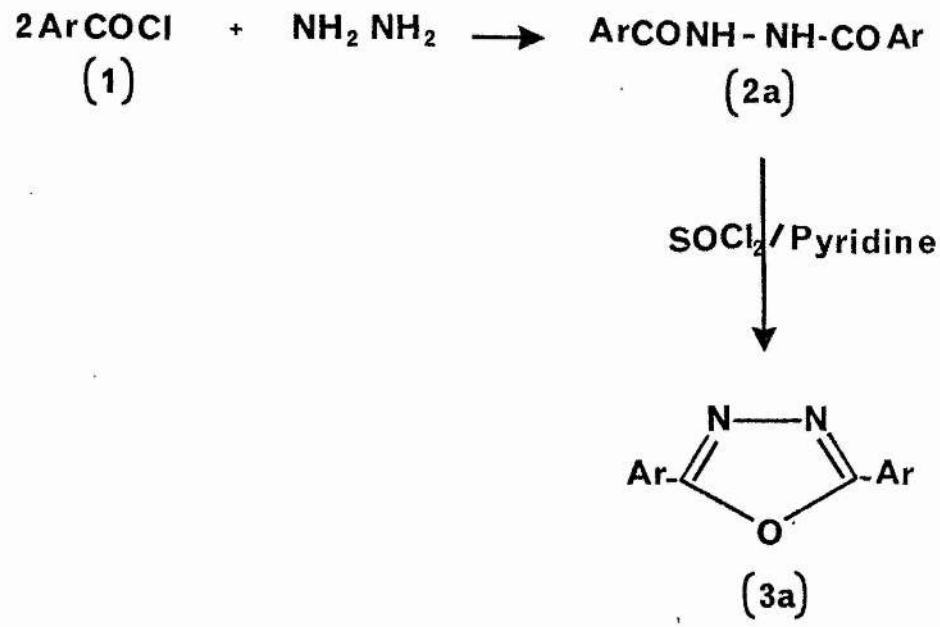
Scheme 1

Heating (2a) above the melting point (180-350°C)[1,36-42] also gives (3a) as does the action of phosphorus pentoxide[40-46], thionyl chloride[40-41] or oxalyl chloride[47] with loss of water. The proposed mechanism of cyclisation in phosphorus oxychloride[48] involves conversion of the diaroylhydrazine to the iminohydroxy tautomer (4) (Scheme 2) which is in equilibrium with the cyclic form (5). Elimination of water from (5) results in the formation of the oxadiazole (3a).



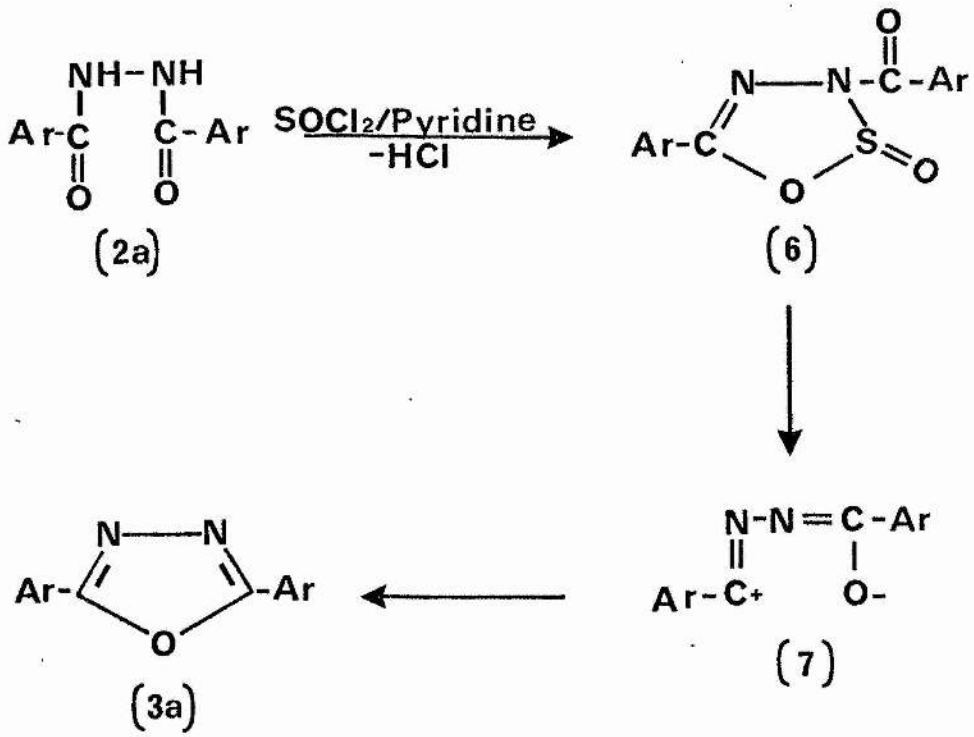
Scheme 2

On heating a diaroylhydrazine in thionyl chloride[49] with a catalytic amount of pyridine, cyclisation of the compound results giving an oxadiazole (Scheme 3).



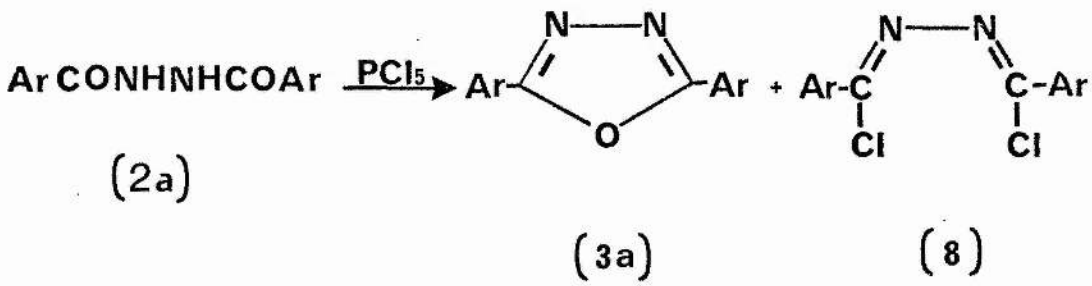
Scheme 3

The probable mechanism for the cyclodehydration of the diaroylhydrazine (2a) in thionyl chloride is shown in scheme 4[49]. The intermediate 1,2,3,4-oxa-thiadiazole-S-oxide (6) undergoes elimination of sulphur dioxide and the resulting charged species (7) undergoes ring closure to give (3a).



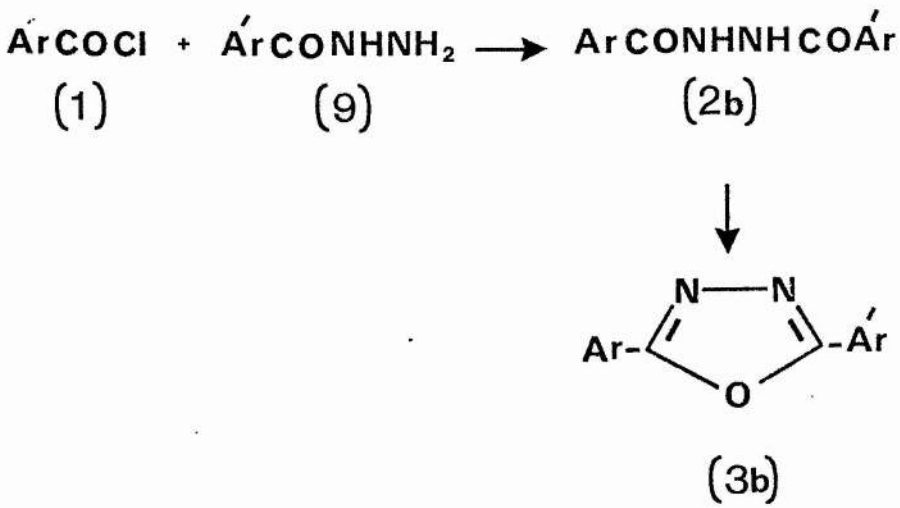
Scheme 4

On heating (2a) with phosphorus pentachloride (8) is obtained as a by-product (Scheme 5)[41,50-53] in addition to (3a).



Scheme 5

Unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles (3b) are prepared[35,54] from an aroyl chloride (1) by reacting it with a monoaroylhydrazine (9) in the presence of a base to give the unsymmetrical diaroylhydrazine (2b) which is cyclised to the oxadiazole (3b) in the usual way (Scheme 6).

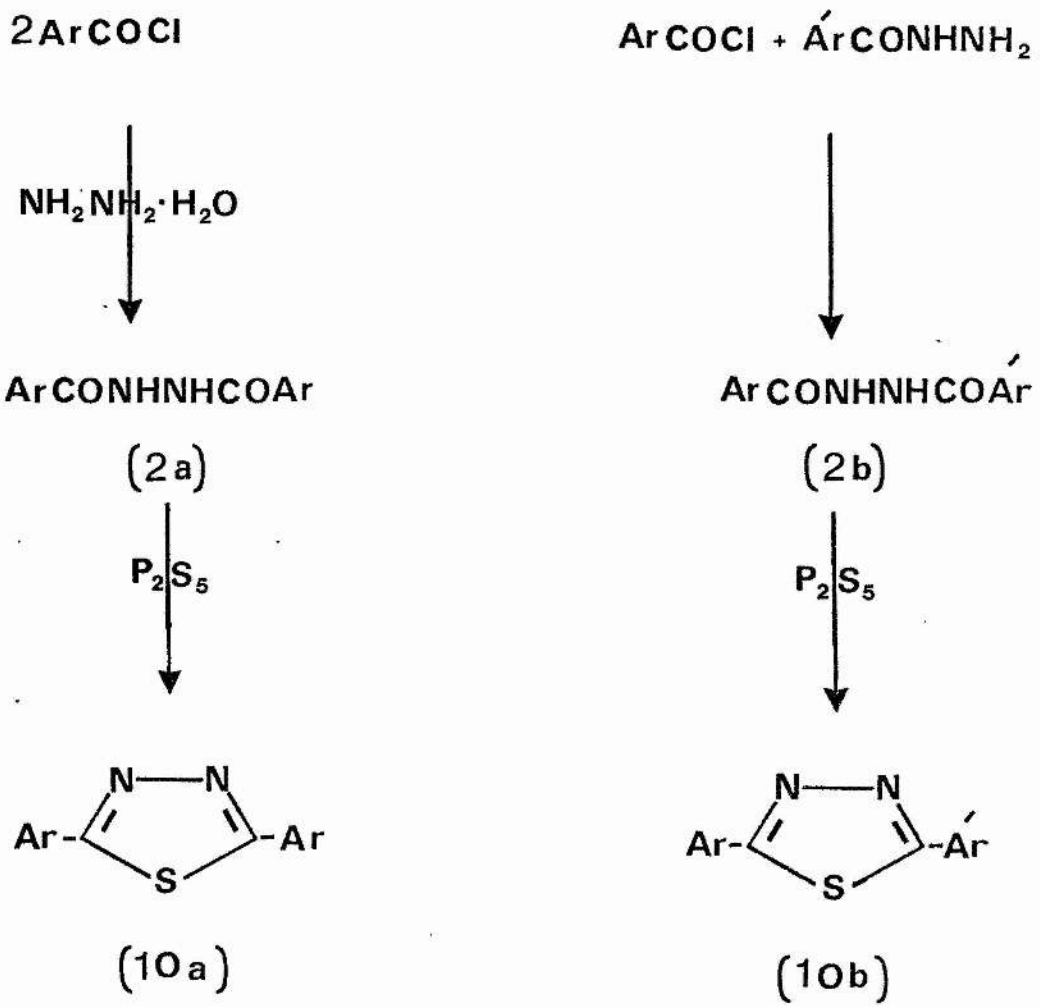


(1) (9) (2b) (3b)

Scheme 6

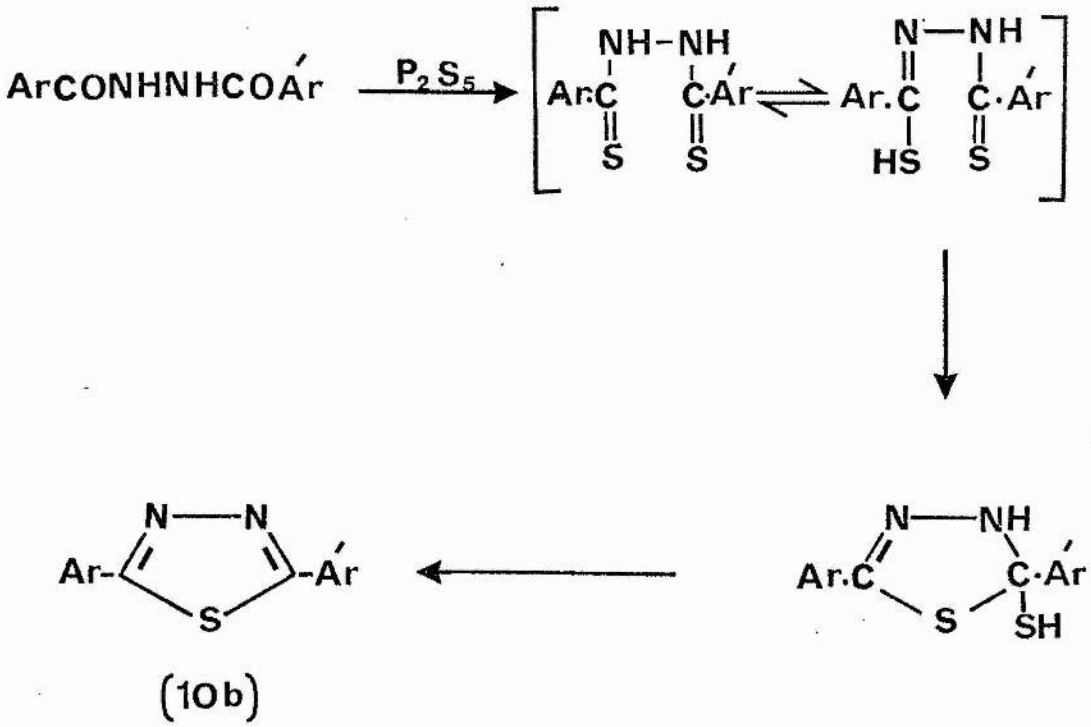
The reaction may be applied to a wide variety of substituted 2,5-diaryl-1,3,4-oxadiazoles and is the method which was generally used in the preparative work described in chapters 2-5.

A general method used by Stollé and collaborators[55-57] for the preparation of 2,5-diaryl-1,3,4-thiadiazole (10a) or (10b) was to treat the diaroylhydrazine (2a) or (2b) with phosphorus pentasulphide. In our case basically the same method was used but was modified to give better yields (Scheme 7).



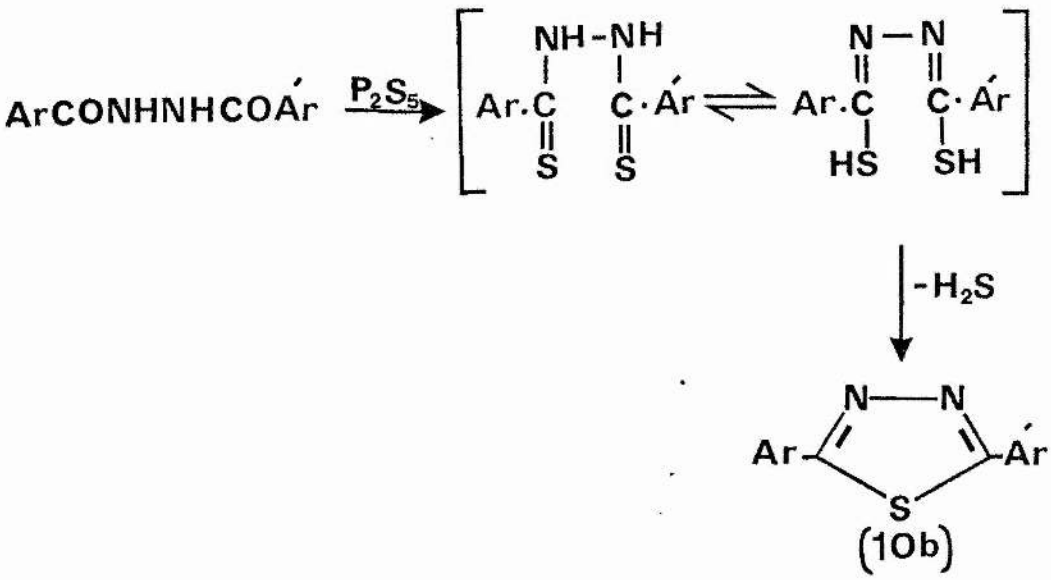
Scheme 7

A possible mechanism proposed for the reaction of diaroylhydrazine (2b) with phosphorus pentasulphide is outlined in Scheme 8[58,59].



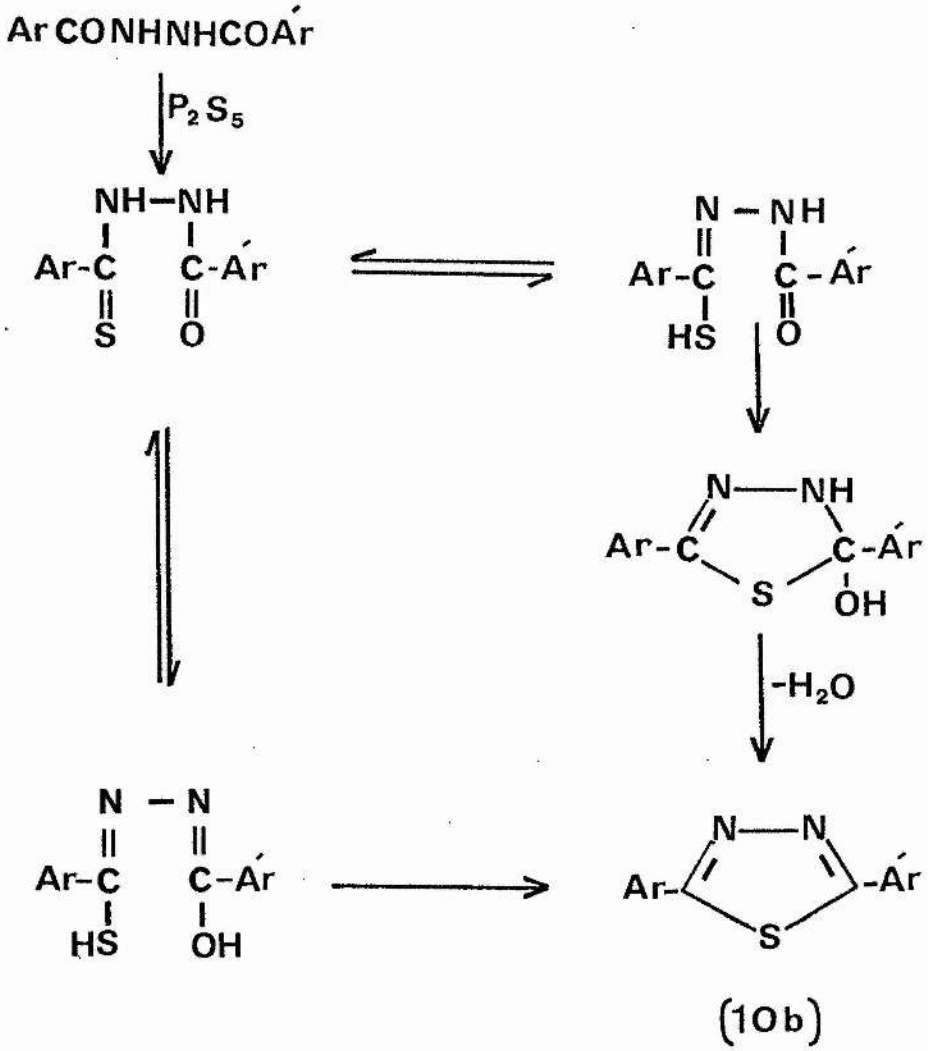
Scheme 8

Another possibility is given in scheme 8a[60].



Scheme 8a

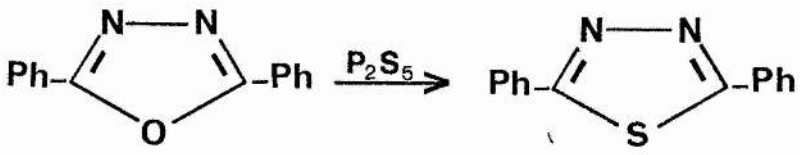
Yet another mechanism may be replacement of only one oxygen by sulphur and elimination of water from the intermediate to give (10b)(Scheme 8b)[5].



Scheme 8b

The unsubstituted 2,5-diphenyl-1,3,4-thiadiazole could be

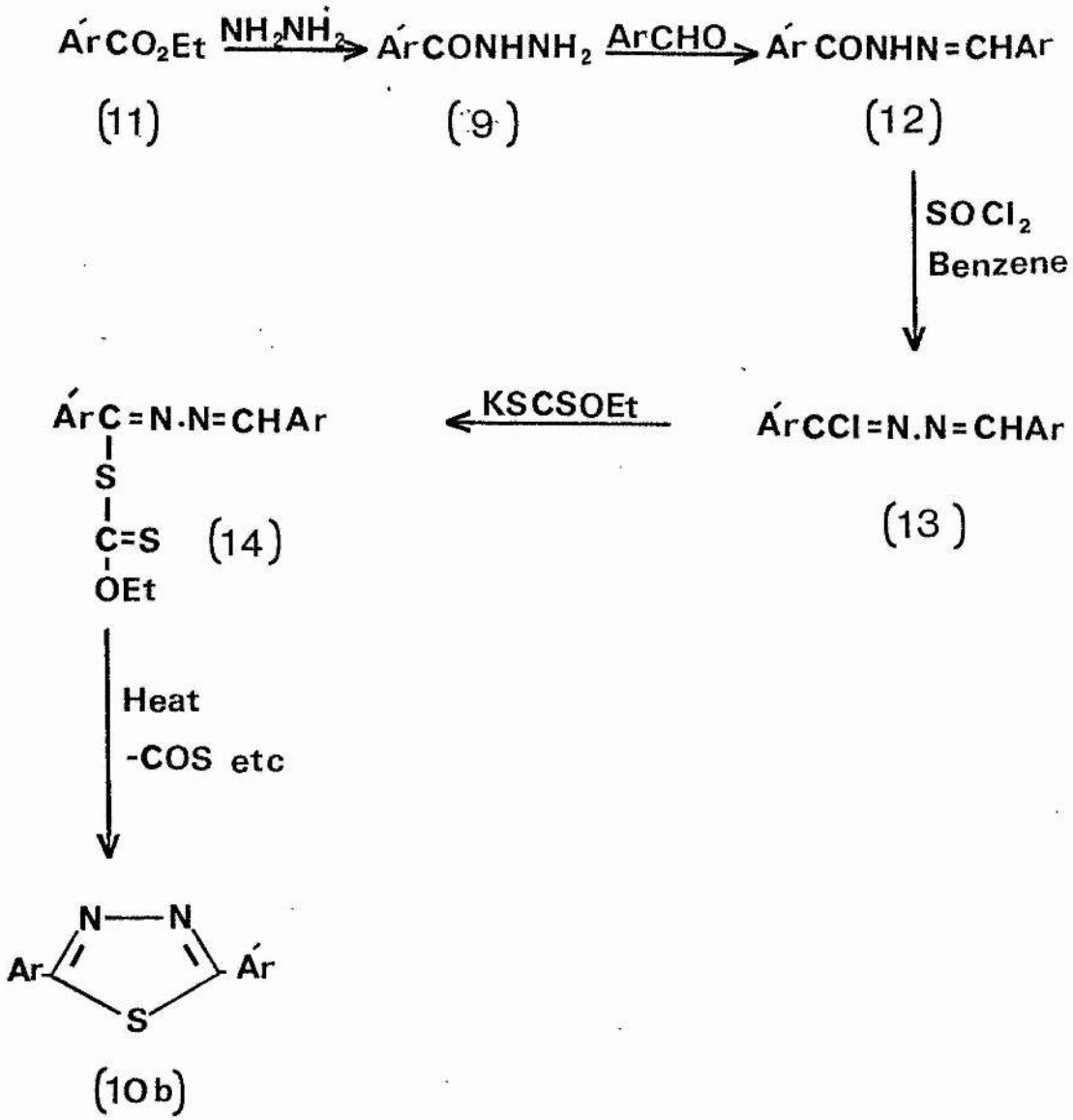
prepared by heating 2,5-diphenyl-1,3,4-oxadiazole with phosphorus pentasulphide in xylene (Scheme 9)[57] .



Scheme 9

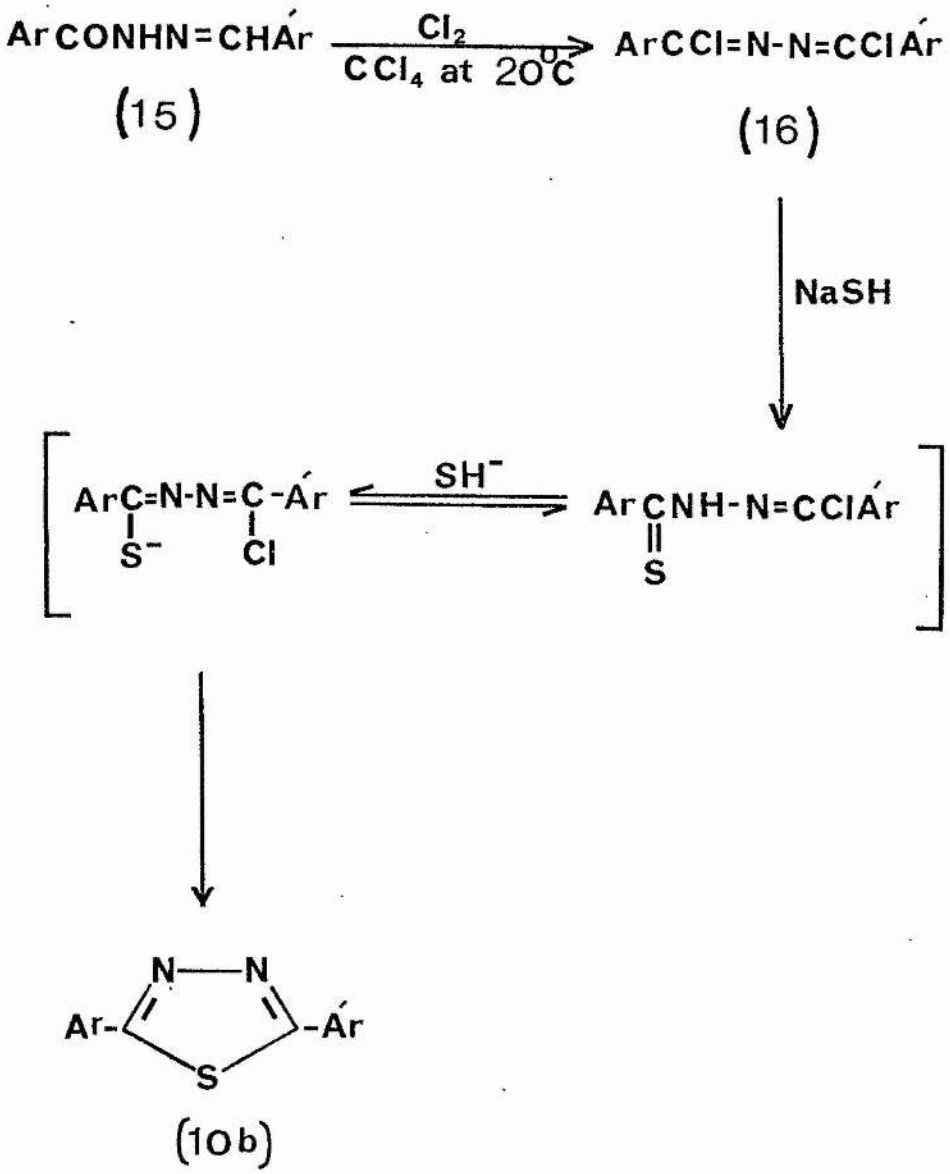
The reaction between 1-chloro-1,4-diaryl-2,3-diazabutadiene (13) and potassium ethyl xanthate on heating in ethanol gives ethyl(1,4-diaryl-2,3-diazabuta-1,3-dien-1-yl)xanthate (14) which on further heating in a sealed tube gives (10b)(Scheme 10)[61].

Monoaroylhydrazines are obtained in the usual way by reacting an ester (11) with hydrazine. The monoaroylhydrazine (9) on reacting with an aldehyde gives (12). The chloroazines (13) were prepared by treatment of the resulting aroylhydrazone with thionyl chloride in benzene.



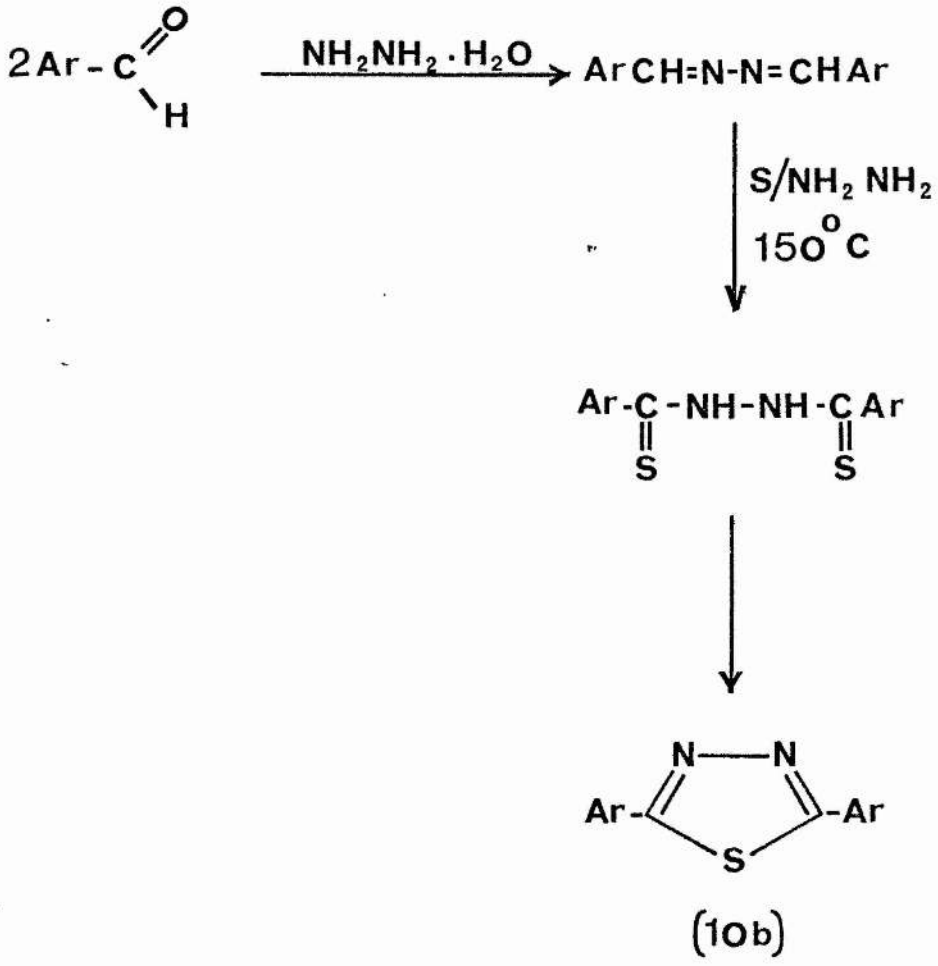
Scheme 10

Scheme 11[62] shows a related route involving 1,4-dichloro-1,4-diphenyl-2,3-diazabutadiene (16) and sodium hydrogen sulphide. (16) is prepared by passing chlorine into a solution of (15) in carbon tetrachloride for two to six hours.



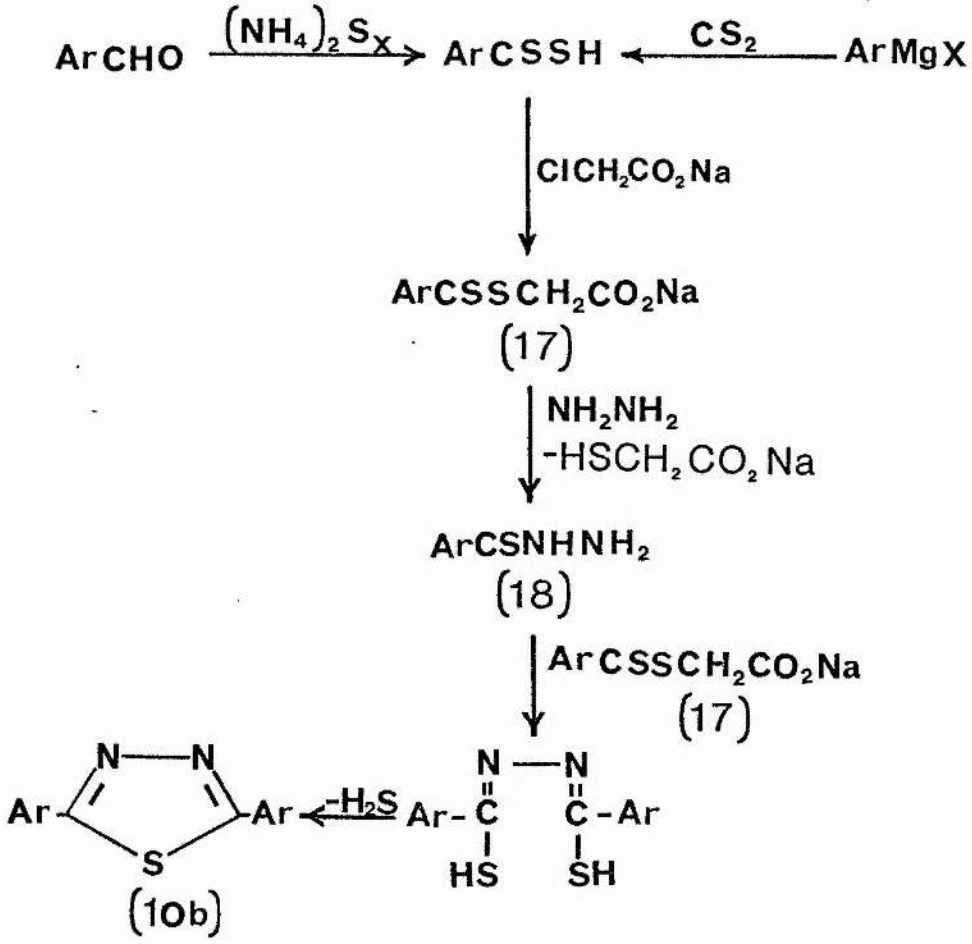
Scheme 11

In another method 1,3,4-thiadiazoles are prepared by treatment of aromatic aldehydes with elemental sulphur and hydrazine hydrate at high temperature and pressure (Scheme 12)[59,63].



Scheme 12

In yet another method dithioacids are first prepared by reacting an aldehyde with ammonium polysulphide; alternatively reacting Grignard compound with carbon disulphide gives a dithioacid. Reacting it with sodium chloroacetate gives the sodium carboxymethyldithiobenzoate (17) which reacts with hydrazine hydrate to give a monothiohydrazide (18). This readily reacts with a second molecule of dithiobenzoate (17) to give a thiadiazole (Scheme 13)[60].



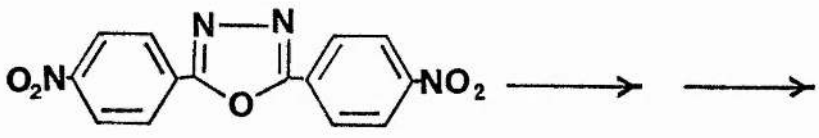
Scheme 13

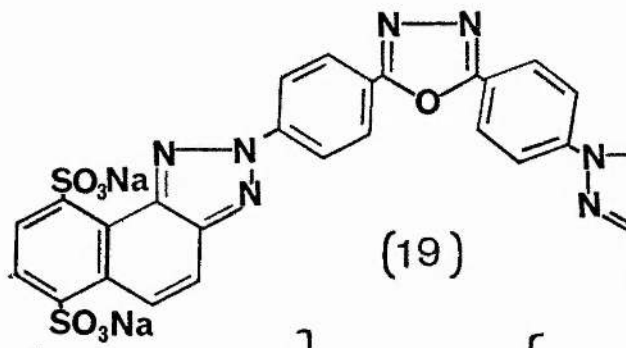
1.3 Substitution Reactions in the Aryl Rings

2,5-Diaryl-1,3,4-oxadiazoles undergo substitution reactions at the aryl residue. Oleum leads to the sulphonic acid derivatives[63,64], in oleum containing bromine, multibromination[65] takes place (one to five bromine atoms in each ring depending on the quantity of bromine and the substituents already present) and with concentrated nitric acid, sulphuric acid/nitric acid mixture or nitronium tetrafluoroborate, nitroaryl compounds are formed[66].

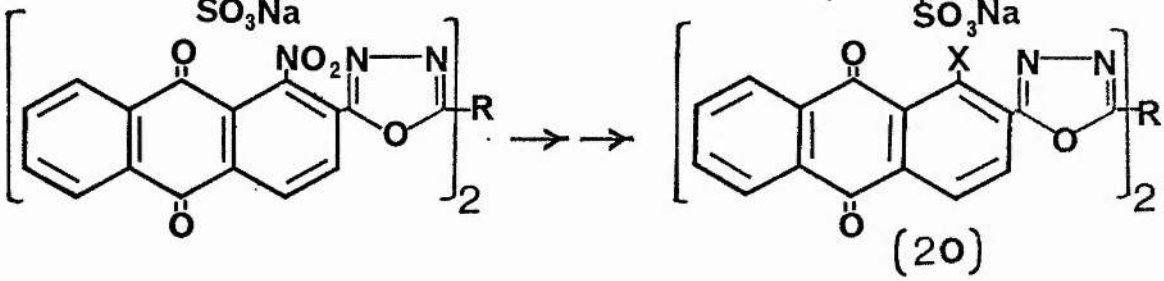
Nitration of 2,5-diphenyl-1,3,4-oxadiazole and -thiadiazole results in the formation of all the six possible isomers. The ratios of ortho,- meta-, and para- isomers vary according to the nitration conditions. The nitration of these compounds and various isomer ratios of the products thereof, will be discussed in the following chapter.

From these nitro compounds, aminophenyl compounds can be prepared in good yields using reducing agents such as iron and hydrochloric acid[18,67]. Diazonium salts are obtained when these amino compounds react with nitrous acid and these show the usual reactions of diazonium compounds[7-9,67] such as coupling and replacement reactions, resulting in compounds like (19) and (20).





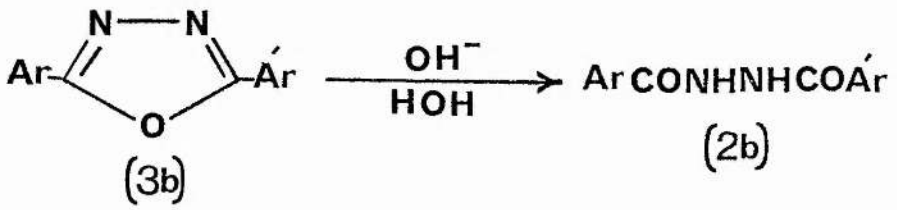
(19)



(20)

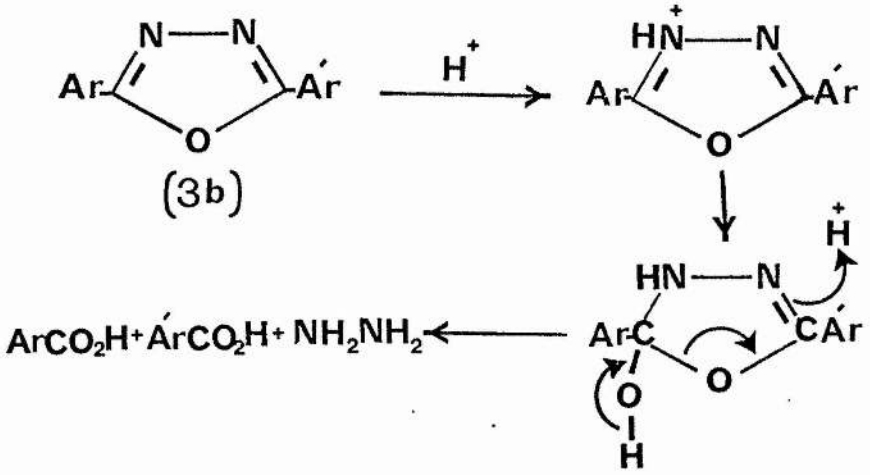
1.4 Reactions Involving Ring Cleavage

2,5-Diaryl-oxadiazoles and -thiadiazoles have a remarkable thermal stability. Some of them can be distilled at temperatures above 300°C without noticeable decomposition. They are not readily attacked by either acids or alkalies. But on prolonged heating with strong nucleophilic reagents like aqueous potassium hydroxide, hydrolysis with ring cleavage occurs to give diaroylhydrazines (2b)(Scheme 14)[54].



Scheme 14

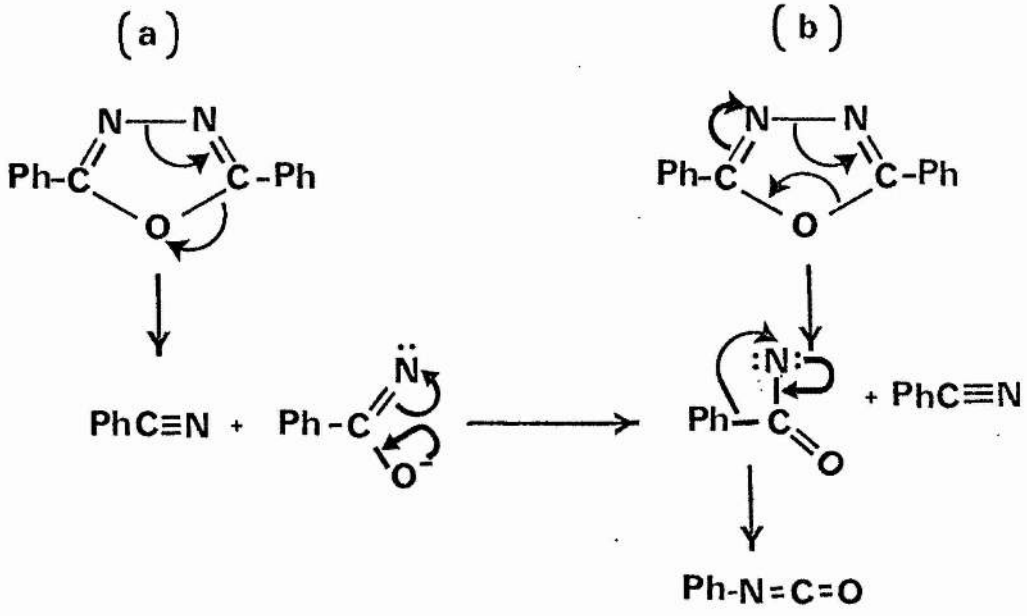
Similarly when heated with 50% hydrochloric acid under reflux for 48 hours, oxadiazoles and thiadiazoles are hydrolysed to their respective acids and hydrazine (Scheme 15)[68].



Scheme 15

1.5 Thermal Decomposition

Pyrolysis of 2,5-diaryl-oxadiazoles in a packed tube at 775°C gives benzonitrile and phenyl isocyanate (Scheme 16a)[69]. Reverse of 1,3- dipolar cyclo-addition is another possibility (Scheme 16b).



Scheme 16

1.6 Electrophilic Substitution of the Phenyl Ring of Phenyl Substituted Heterocyclic Compounds

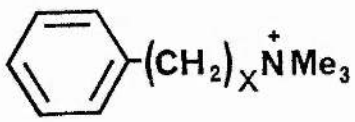
Orientation of the incoming electrophile (ortho-, meta-, para-) in an electrophilic substitution of a phenyl ring depends on the substituent(s) already present and their overall directing properties.

The partial positive and negative charges at the ring carbon produced by the electronegativity of the substituent is known as the inductive effect of the substituent. This may be either

a) positive (+I): electron donating and ortho-/para-directing;

or b) negative (-I):electron withdrawing and meta-directing.

If the substituent carries positive charge[70,71] the static effect could be profound. If the charged atom is adjacent to the phenyl ring the substituent has a -I effect and is meta-directing, but the effect falls off with increasing number of carbon atoms separating the charged centre from the phenyl ring, e.g.



when x=0 meta-isomer 89 %,

x=1 " " 85-88 %,

x=2 " " 19 %,

x=3 " " 03 %.

When the π-orbital of the phenyl group overlap with a p-orbital, a hybrid of p-type or another π-orbital on an adjacent atom delocalisation may result. When the delocalisation results in increase of electron density on the phenyl ring through conjugation the effect is termed as

a) positive mesomeric effect (+M) and the substituent is ortho-/para- directing.

The substituents which result in a decrease of electron density on the phenyl ring are termed as having a

b) negative mesomeric effect (-M) and have meta-directing effect.

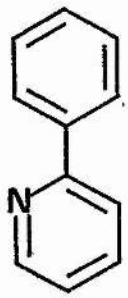
If the substituent is another phenyl ring, by its conjugation through π-orbitals it is expected to be ortho-/para-directing. This is in agreement with the experimental results[72]. Even in the case of 2,4-dinitrobiphenyl[72], where the dinitrophenyl ring would not be expected to stabilise a positive charge easily, ortho- and para-nitration still takes place. Of course, if the effect of the phenyl or dinitrophenyl substituent is to be mesomeric at all, the two rings must be coplanar (or almost so) in the transition state. Otherwise the effect of the substituent has to be regarded as inductive only. If the phenyl ring has a heterocyclic ring as a substituent, then in addition to existing mesomeric and/or inductive effects the heteroatom itself may

create an additional complication. If the heteroatom is a basic or nucleophilic nitrogen, it may be protonated in acidic media, or may react itself with the electrophile. These protonated/quaternised heterocycles may exert a different effect on the phenyl ring compared with the unprotonated/unquaternised substituent.

To understand fully the electrophilic substitution of 2,5-diphenyl-1,3,4-thiadiazole and -oxadiazole, it is necessary to determine whether the heterocyclic ring bears a positive charge or not under the different conditions of reaction.

The electrophilic substitution of some other phenyl substituted heterocycles have previously been studied by other groups. Some of their results are reproduced below.

Katritzky and Kingsland[73] and De Sarlo and Ridd[74] investigated the nitration of 2-phenylpyridine (21) and its N-oxide and 4-phenylpyridine (22).



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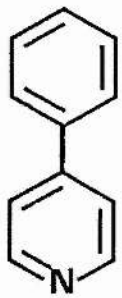


(22)

The former group found that the nitration of (21) in 92%

sulphuric acid results in an ortho: meta: para isomer ratio of 9:39:52 and nitration of the N-oxide of (21) in 81% sulphuric acid gave 17% para- isomer, more than 80% meta-isomer, less than 3% ortho-isomer. De Sarlo and Ridd while nitrating (22) in 98% sulphuric acid got ortho- 20%; meta- 33%; para- 47%.

The conclusions of De Sarlo and Ridd, on the basis of their results and taking into account the results of Katritzky and Kingsland, are that the nitration of 2- and 4-phenylpyridines takes place on conjugate acids, and all positions are strongly deactivated with respect to benzene.

The pattern can be explained by assuming that the inductive and field effects are partly compensated by a +M effect.

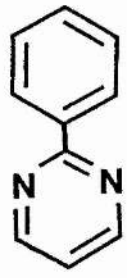
Katritzky and Kingsland concluded from their investigations that the partial rate factors are similar to those for the benzyltrimethylammonium cation and that inductive and /or direct field effects are of predominant importance with mesomeric effect playing a secondary role in these nitrations.

In a paper Johnson, Katritzky and Viney[75] have discussed the nitration of pyridines in sulphuric acid solutions and their conclusions were that more basic pyridines ($pK_a > +1$) are nitrated as cations and very weakly basic pyridines ($pK_a < -2.5$) undergo nitration as free bases and nitrate more easily. Somewhere in between pK_a +1.0 and -2.5 a changeover in mechanism and reactivity must occur.

Katritzky and Simons[76] have published pK_a's of phenylpyridines and their N-oxides. Phenylpyridines have pK_a's between 4.5 and 5.5 while the N-oxides are weaker bases with pK_a's between 0.7 and 0.8. Nevertheless kinetic work indicated that the N-oxides are also nitrated as their conjugate acids[73].

In the case of phenylpyrimidines the situation is different. Nitration of 2-phenylpyrimidine (23) apparently gives the meta-nitro-isomer (24) as the main product[77]. This could be explained in terms of the -I effect of a positively charged substituent (cf. p.18). When the two nitrogens are differently positioned with respect to the phenyl ring, as in 4-phenylpyrimidine, interpretation is more complicated.

Lynch and Poon[78] and Adam, Doranjh, and Hurst[79] investigated the nitration of 4-phenylpyrimidine (25) with fuming nitric acid and concentrated sulphuric acid and obtained two isomers: 4-o-nitrophenyl- and 4-m-nitrophenylpyrimidine in the ratio of 40:60. The p-nitrophenyl-isomer was not detected. However with nitric acid in trifluoroacetic anhydride all three isomers were found in the ratio ortho: meta: para = 45: 29: 26.



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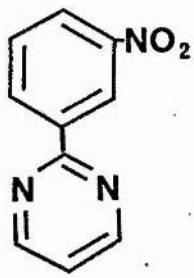

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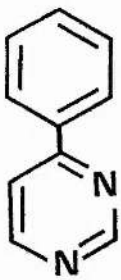

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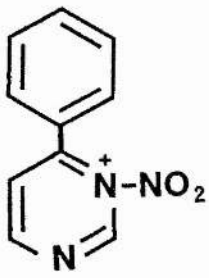
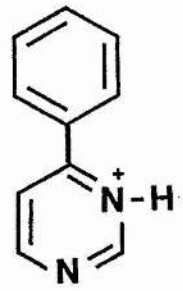


(26)

The absence of para-nitro-isomer in these cases is unusual. The previous authors'[78,79] explanation for these results was that in nitric acid and sulphuric acid an N-nitronium species (26) is formed at N-3 of the pyrimidine and this species is attacked directly at the meta- position due to the 'positive pole' (-I) effect. The formation of ortho-isomer is explained by (26) dissociating into nitronium ion (NO_2^+) and 4-phenylpyrimidine and then intramolecular attack of (NO_2^+) at the adjacent ortho-position on the phenyl ring.

With nitric acid in trifluoroacetic anhydride their suggestion was that (26) adds a trifluoroacetate ion to yield (27) in which the heterocycle is then an ortho-/para- directing substituent. The nitration of (25) is then regarded as proceeding in part via (26) (giving ortho- and meta- nitration) and also via (27) (giving ortho- and para-nitro compounds).



(28)

(27)

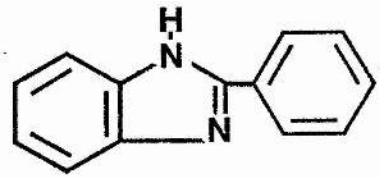
We suggest that in nitric acid and sulphuric acid, nitration may be partly taking place on the protonated species (28) which due to the 'positive pole' effect gives meta-substitution, and partly by way of (26) and transfer of nitronium ion (NO_2^+) intramolecularly to give the ortho-isomer.

We further suggest that the results obtained in the case of nitric acid in trifluoroacetic anhydride can best be explained if we suppose that the nitration is taking place partly on the uncharged molecule (25) and partly on the N-nitronium cation (26).

The effect of heteroatom(s) in five membered rings on substitution of an attached phenyl ring may vary from those in the six membered rings. Not only is the geometry of a five membered ring quite different from a benzenoid ring but also when it contains hetero-atoms its charge distribution differs as well. The following survey is confined to ring systems where the phenyl group(s) is/are attached to carbon atom(s) and where nitration in the heterocyclic ring is not competing with the substitution in the phenyl ring(s).

Literature[80] contains several examples of electrophilic substitution of phenyl substituted five membered rings such as pyrazoles, imidazoles and triazoles. In most cases the para-nitro-isomer is the only product reported. It is not clear whether it was the only product formed or the only one isolated. In our experience para-isomers are almost always the least

soluble and come out first, whenever crystallisation is carried out. If the para-isomer(s) is/are the major product(s), the other isomers are left behind in the mother liquor.



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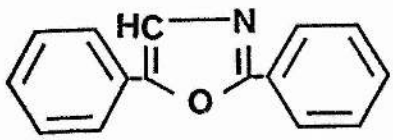
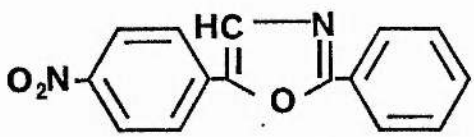


(30)

The results obtained by nitrating 2-phenylbenzimidazole (29)[81] in nitric acid and nitric acid and sulphuric acid show no variation in isomer ratio ortho-: meta-: para $\simeq$ 1:2:4. The authors concluded from these results that the same species was involved in both nitrations. Compound (29) is a relatively strong base (it has a pK_a of 5.23) and it is known[82] that (29) undergoes electrophilic substitution in acidic media as the conjugate acid. The isomer ratio is obviously very different from that of the 2-phenylpyrimidine nitration although the positions of the hetero-atoms with respect to the phenyl ring are similar.



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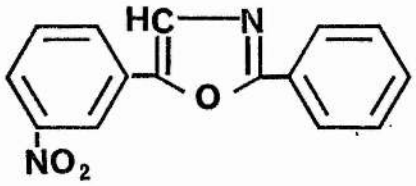

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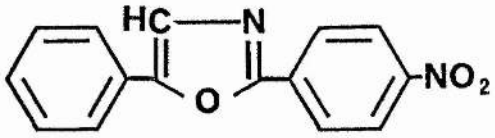


(33)

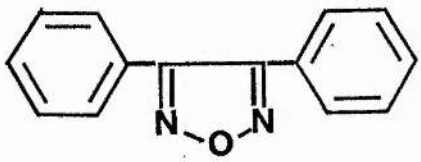
The nitration of 2,5-diphenyloxazole (30) was carried out by Lister and Robinson[83] and by Minovici[84] in fuming nitric acid at 0°C for 0.5 hour. They obtained a quantitative yield of 5-(p-nitrophenyl)-2-phenyloxazole (31).

Nitration of 2,5-diphenyloxazole (30) was reinvestigated by Sagar and Smith[65] and the previous results obtained[83,84] under the same conditions were confirmed by them. They furthermore found that if the reaction time was increased to two hours both phenyl rings were nitrated and that nitration of the 2-phenyl group gave all three isomers in which the para-isomer was predominant.

As is obvious from the structure of compound (30) , the two phenyl rings are non-equivalent, one nearer to the basic centre than the other. The phenyl ring attached to C-2 could be treated

as in a similar environment to that of the phenyl ring(s) of 2-phenylbenzimidazole as well as 2,5-diphenyl-1,3,4-oxadiazole and -thiadiazole which will be discussed in chapter 2. The ortho: meta: para ratio for nitration of the phenyl ring (attached to C-2) in the oxazole is also similar to that of the phenylbenzimidazole.

Zeknov, Frolova, Mel'nikova and Tselinskii[85] nitrated 3,4-diphenyl-1,2,5-oxadiazole (34) in fuming nitric acid and also with nitronium tetrafluoroborate. In both cases they obtained after recrystallisation 3,4-bis(p-nitrophenyl)-1,2,5-oxadiazole (77%). On the other hand nitration of (34a) with nitric acid and sulphuric acid apparently gave the meta-nitro- compound (97%). Other isomers in these reactions if they were present would be lost on recrystallisation and would probably remain in the mother liquor.



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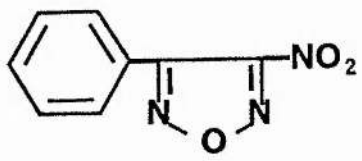


(34a)

From the foregoing it is apparent that the results of electrophilic substitution of various systems can be rationalised and explained in individual cases, but are not such that a hard

and fast general rule of directive effect can be framed with the present information and knowledge. A lot of work has yet to be done before a definite quantitative prediction of directive effects can be made for various heterocyclic substituents on a phenyl ring.

Table 1

RESULTS OF NITRATION OF SOME HETEROCYCLIC COMPOUNDS

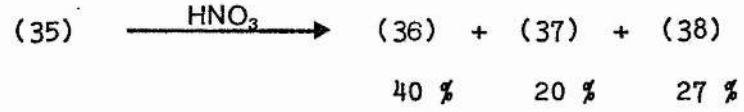
	Compounds	Nitration Medium	p- %	m- %	o- %
i)	2-phenylpyridine	92% H_2SO_4/HNO_3	52	39	9
ii)	2-phenylpyridine	81% H_2SO_4/HNO_3	17	>80	<3
iii)	4-phenylpyridine	98% H_2SO_4/HNO_3	47	33	20
iv)	2-phenylpyrimidine	H_2SO_4/HNO_3	-	100	-
v)	4-phenylpyrimidine	H_2SO_4/HNO_3	-	40	60
vi)	4-phenylpyrimidine	$(F_3CCO)_2O/HNO_3$	45	29	26
vii)	2-phenylbenzimidine	1. HNO_3 2. H_2SO_4/HNO_3	60	26	14
iix)	5-(p-nitrophenyl)-2-phenyloxazole	HNO_3	78	10	12
ix)	5-(p-nitrophenyl)-2-phenyloxazole	H_2SO_4/HNO_3	70	20	10
x)	5-(m-nitrophenyl)-2-phenyloxazole	HNO_3	79	11	10
xi)	5-(m-nitrophenyl)-2-phenyloxazole	H_2SO_4/HNO_3	78	10	12

CHAPTER 2

Nitration: Results and Discussion

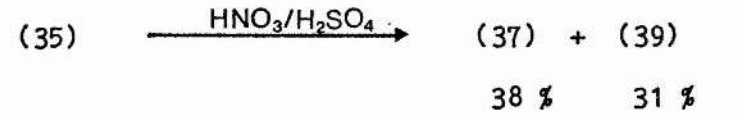
2.1 Nitration of 2,5-diphenyl-1,3,4-oxadiazole

One of the two reports on the nitration of 2,5-diphenyl-1,3,4-oxadiazole (35) is by Grekov and Azen[86] who claimed to have obtained three symmetrical dinitro-isomers (36-38)(Scheme 17) by nitration in fuming nitric acid (d 1.51).

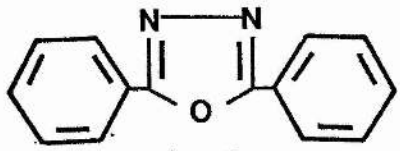


Scheme 17

In concentrated sulphuric acid (d 1.84) and fuming nitric acid only two products were apparently obtained by them: 2,5-bis(m-nitrophenyl)-1,3,4-oxadiazole (37) and 2-(m-nitrophenyl)- 5-phenyl-1,3,4-oxadiazole (39) (Scheme 18).



Scheme 18



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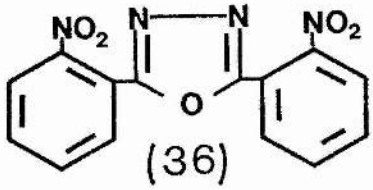

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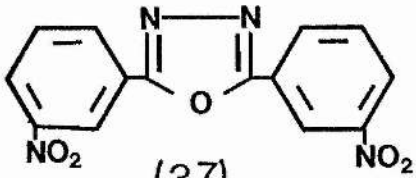

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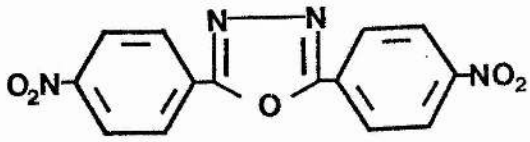

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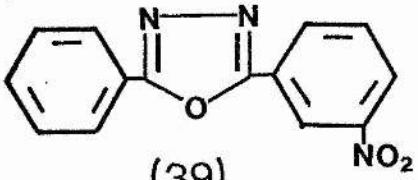

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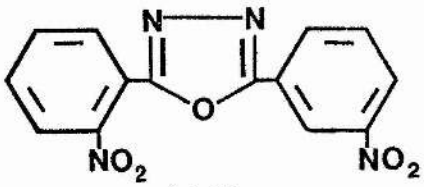

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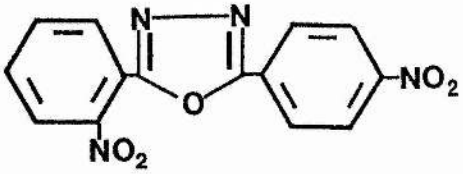

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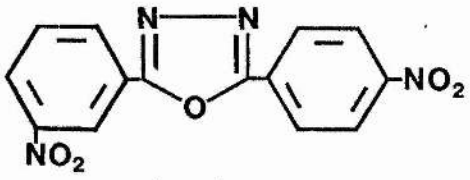

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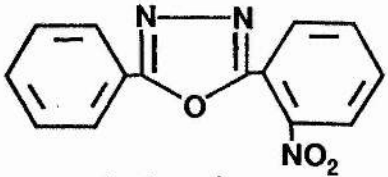

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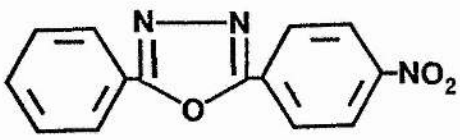
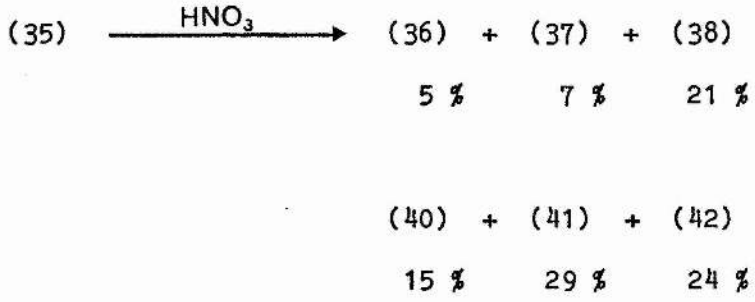


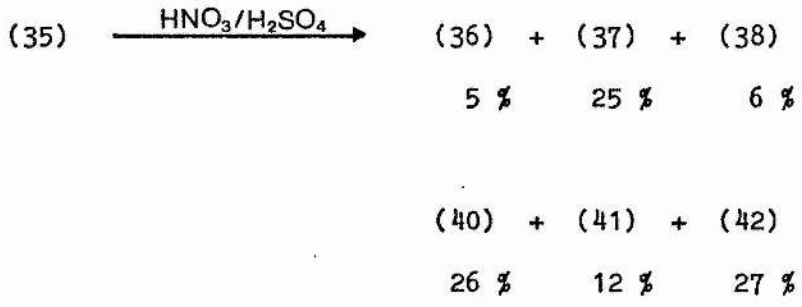
(44)

When this claim was reinvestigated however, by the St. Andrews research group[65,66] using high performance liquid chromatography for separation and quantification of these products, it was established that not only had the Russians[86] miscalculated the yields (see footnote Ref. 66, p. 774) but they had also failed to separate all the isomers. All the six possible isomers (36-38 and 40-42) were obtained when (35) was nitrated with fuming nitric acid (d 1.5) (Scheme 19) [65,66].



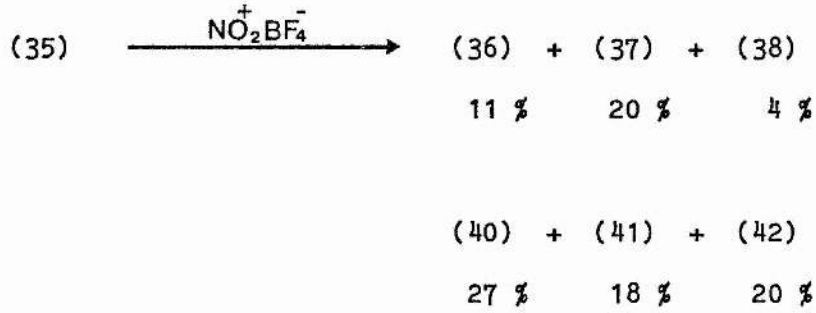
Scheme 19

Changing from fuming nitric acid to a concentrated sulphuric acid and nitric acid mixture gave the same six isomers, although the percentage of meta-nitration increased and consequently the percentage of para-isomers decreased (Scheme 20) but no mono-nitro- isomer was detected.



Scheme 20

Similarly when the authors[65,66] tried nitronium tetrafluoroborate in sulpholane as the nitrating medium, they again obtained increased yields of meta-nitro-isomers and also increased yields of ortho- nitro-isomers (Scheme 21).



Scheme 21

To understand more about these nitrations, the three mono-nitro-isomers (39), (43) and (44) were synthesised and nitrated under similar conditions to those used for (35). These nitration results are summarised in tables 2-5.

Table 2

Nitration of 2,5-diphenyl-1,3,4-oxadiazole

Nitrating Agent(s)	Isomer % 2,2'	2,3'	2,4'	3,3'	3,4'	4,4'
HNO_3	5	15	29	7	24	20
HNO_3/H_2SO_4	5	26	12	25	27	6
$NO_2^+ BF_4^-$	11	27	18	20	20	4

Table 3

Nitration of 2-phenyl-5-(o-nitrophenyl)-1,3,4-oxadiazole

Nitrating Agent(s)	Isomer % 2,2'	2,3'	2,4'
HNO_3	19	34	47
HNO_3/H_2SO_4	15	67	18
$NO_2^+ BF_4^-$	39	20	41

Table 4

Nitration of 2-phenyl-5-(m-nitrophenyl)-1,3,4-oxadiazole

	Isomer %		
Nitrating Agent(s)	2,3'	3,3'	3,4'
HNO_3	26	29	45
HNO_3/H_2SO_4	22	60	18
$\overset{+}{N}O_2\,\overset{-}{B}F_4$	35	36	29

Table 5

Nitration of 2-phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole

	Isomer %		
Nitrating Agent(s)	2,4'	3,4'	4,4'
HNO_3	34	23	43
HNO_3/H_2SO_4	22	60	18
$\overset{+}{N}O_2\,\overset{-}{B}F_4$	50	19	30

From tables 2-5 the following observations were made by the team[65] who carried out these nitration studies.

i) There was no starting material found among the nitration products;

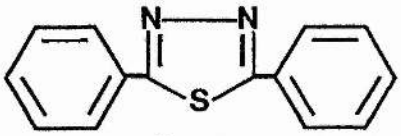
ii) There was a large variation in the isomer ratio according to the nitrating medium used;

iii) Enhancement of meta-nitration took place at the expense of para-nitration as the nitrating medium was changed from nitric acid, through nitric acid and sulphuric acid, to nitronium tetrafluoroborate;

iv) In the reaction involving nitronium tetrafluoroborate there was an increase in ortho-nitration.

In order to find out if, during nitration of 2,5-diphenyl-1,3,4-oxadiazole (35), the two nitration steps leading to mono- and dinitro-isomers were independent or concurrent, a semikinetic experiment with fuming nitric acid as the nitrating medium was undertaken by the same team[65]. From the experiment it was concluded that the first and second nitration steps are almost independent of each other, the first being much faster than the second.

On the basis of these results (table 2-5), the ratio of the mononitro-isomers produced during the nitration of (35) could be calculated. The results are as follows:-



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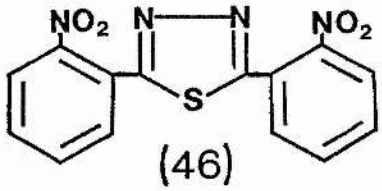

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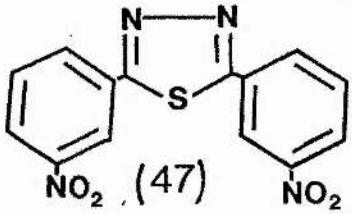

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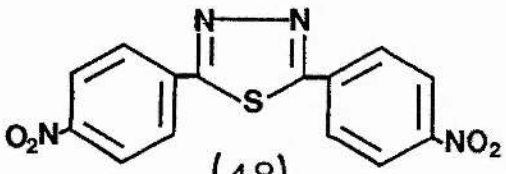

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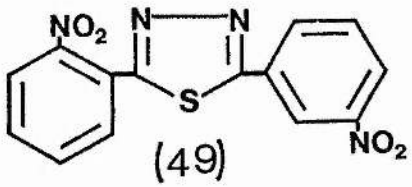

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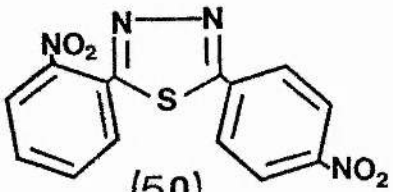

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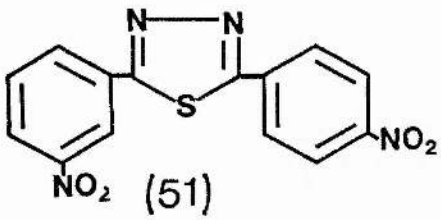

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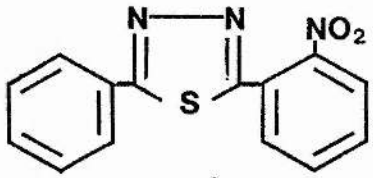

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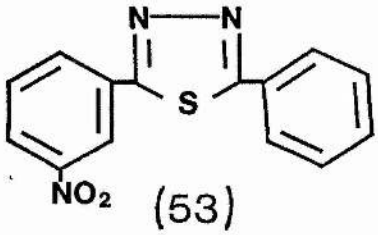

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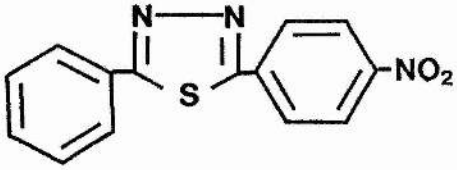


(54)

Table 6

Mononitration of 2,5-diphenyl-1,3,4-oxadiazole

Nitrating Agent(s)	Isomer % ortho-	meta-	para-
HNO_3	25	25	50
HNO_3/H_2SO_4	26	41	33
$NO_2^+BF_4^-$	29	58	13

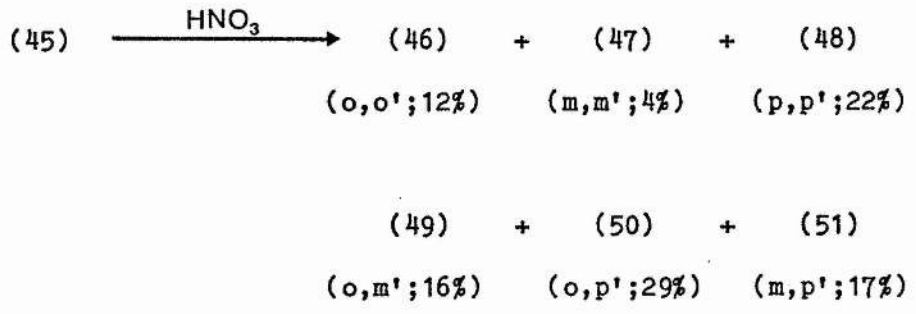
2.2 Nitration of 2,5-diphenyl-1,3,4-thiadiazole and its mononitro-derivatives.

Since systems considered so far (Chapter 1) were not exactly similar to 2,5-diphenyl-1,3,4-oxadiazole (35) either structurally or in their behaviour towards electrophilic substitution the present investigation for the nitration of 2,5-diphenyl-1,3,4-thiadiazole (45) was instituted in order to give more insight into the mechanism of nitration under various conditions.

2.2.1 Nitration of 2,5-diphenyl-1,3,4-thiadiazole

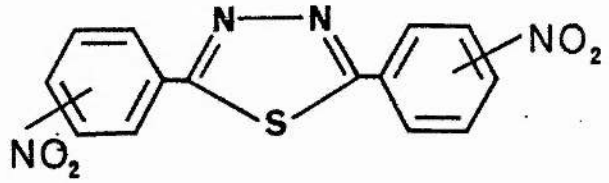
The general method used for the preparation of 2,5-diphenyl-1,3,4-thiadiazole (45) has already been outlined in scheme 7(p.7)[57].

In order to compare the results of nitration of (35) with (45), nitration of (45) was carried out by similar methods as used for the nitration of 2,5-diphenyl-1,3,4-oxadiazole (35) using different nitrating agents viz. fuming nitric acid (d 1.5), concentrated sulphuric acid (d 1.84) and nitric acid (d 1.5) and nitronium tetrafluoroborate in sulpholane. All the six possible dinitro-isomers (46-51) were obtained and were separated cleanly as six peaks (Figure 1) by h.p.l.c. No mononitro-compound was observed (Scheme 22). The mono- and dinitro-compounds were synthesised independently by the same general route as used for (45) (Scheme 7)[57].



Scheme 22

LIQUID CHROMATOGRAM OF



COMPOUNDS

FIGURE 1

Scale 1 cm = 1 Min.

(46)

(49)

(50)

(47)

(51)

(48)

-40-

Absorbance

Time

Changing from fuming nitric acid to a stronger medium such as nitric acid and sulphuric acid again resulted in the formation of all the six possible isomers though there was a definite increase in the percentage yield of meta-nitro-isomers (Scheme 23) at the expense of para-nitrated products.

(45) $\xrightarrow{HNO_3/H_2SO_4}$ (46) + (47) + (48)

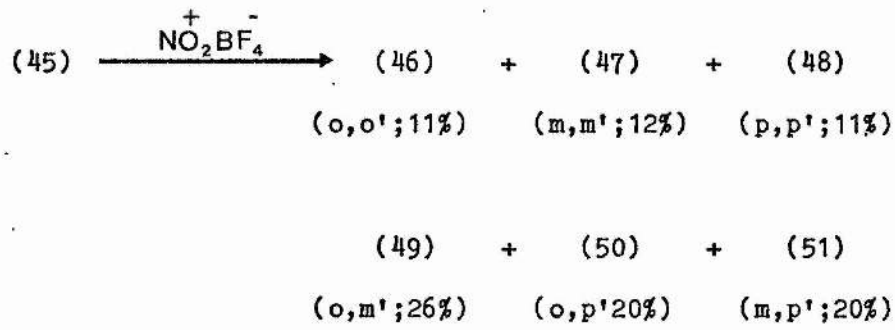
(o,o';10%) (m,m';8%) (p,p';16%)

(49) + (50) + (51)

(o,m';20%) (o,p';25%) (m,p';21%)

Scheme 23

Similarly when nitration of (45) was carried out with nitronium tetrafluoroborate in sulpholane (Scheme 24) again enhancement of meta-nitro-isomers was observed at the expense of the para- analogue. There was a small amount of mononitro-isomers (<1.0%).



Scheme 24

The results of nitration of 2,5-diphenyl-1,3,4-thiadiazole (45) in different nitrating media are collected in table 7.

Table 7

Nitration of 2,5-diphenyl-1,3,4-thiadiazole

	Isomer %					
Nitrating Agent(s)	2,2'	2,3'	2,4'	3,3'	3,4'	4,4'
HNO_3	12	16	29	4	17	22
HNO_3/H_2SO_4	10	20	25	8	21	16
$NO_2^+BF_4^-$	11	26	20	12	20	11

2.2.2 Nitration of the mononitro-derivatives

Nitration of mononitro-isomers (52-54) under the same conditions as before was carried out using different nitrating media. The results are listed in tables 8-10. The yields are essentially quantitative in each case.

The noticeable feature of these results is again the increase in the proportion of meta-nitration as the nitrating medium is changed from nitric acid to nitric acid in sulphuric acid and nitronium tetrafluoroborate.

Table 8

Nitration of 2-phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole(52)

	Isomer %		
Nitrating Agent(s)	2,2'	2,3'	2,4'
HNO_3	36	32	32
HNO_3/H_2SO_4	29	41	30
$NO_2^+BF_4^-$	33	47	20

Table 9

Nitration of 2-phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole(53)

	Isomer %		
Nitrating Agent(s)	2,3'	3,3'	3,4'
HNO_3	36	26	38
HNO_3/H_2SO_4	36	30	34
$\overset{+}{NO_2}\overset{-}{BF_4}$	35	41	24

Table 10

Nitration of 2-phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole(54)

	Isomer %		
Nitrating Agent(s)	2,4'	3,4'	4,4'
HNO_3	32	20	48
HNO_3/H_2SO_4	31	28	41
$\overset{+}{NO_2}\overset{-}{BF_4}$	34	36	30

If it can be assumed that the two nitrations of 2,5-diphenyl-1,3,4-thiadiazole (45), like those of its oxadiazole analogue (35), are independent of each other, it is possible to calculate isomer ratios for the first nitration of the thiadiazole (45). These are shown below (Table 11).

Table 11

Mono-nitration of 2,5-diphenyl-1,3,4-thiadiazole

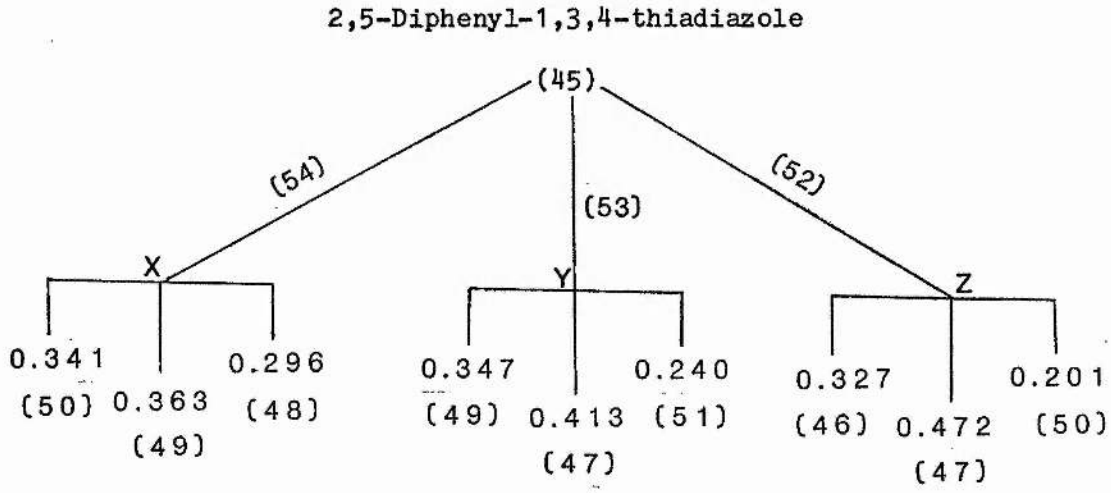
(Inferred from the results of tables 7-10)

	Isomer %		
Nitrating Agent(s)	ortho-	meta-	para-
HNO_3	34	15	51
HNO_3/H_2SO_4	33	23	44
$\overset{+}{NO_2}\overset{-}{BF_4}$	34	29	37

The method of calculation is detailed in figure 2.

Figure 2

Nitration of 2,5-diphenyl-1,3,4-thiadiazole in nitronium Tetrafluoroborate



$0.296x = 0.111$ (1)

$0.413y = 0.117$ (2)

$0.327z = 0.110$ (3)

$0.341x + 0.201y = 0.195$ (4)

$0.363x + 0.240z = 0.202$ (5)

$0.347y + 0.472z = 0.265$ (6)

from (1) $x = 0.111/0.296$

$= 0.375$

from (2) $y = 0.117/0.413$

$= 0.283$

from (3) $z = 0.110/0.336$

$= 0.336$

from (4) by dividing with 0.341; and from (5) by 0.363 we get,

$$x + 0.589z = 0.572 \quad (7)$$

$$\underline{x + 0.661y = 0.556} \quad (8)$$

By substracting $-0.661y + 0.589z = 0.016$ (9)

from (6) we get $y + 1.360z = 0.764$ (11)

from (9) we get $-y + 0.891z = 0.024$ (12)

by adding (11 & 12) $2.251z = 0.788$

$$z = 0.788/2.251$$

$$= 0.350$$

By putting value of z in (7) we get,

$$x = 0.572 - 0.206$$

$$= 0.366$$

By putting the value of z in (11) we get,

$$y = 0.764 - 0.476$$

$$= 0.288$$

Therefore average value of

$$x = (0.375 + 0.366)/2$$

$$= 0.371 \quad = 37\ \%$$

$$y = (0.283 + 0.288)/2$$

$$= 0.286 \quad = 29\ \%$$

$$z = (0.350 + 0.336)/2$$

$$= 0.343 \quad = 34\ \%$$

If we compare tables 2-6 with 7-11, it becomes obvious that in the case of 2,5-diphenyl-1,3,4-thiadiazole (45) vis-à-vis 2,5-diphenyl-1,3,4-oxadiazole (35), there is very much less variation in isomer ratios as the nitrating medium is changed. In this respect the behaviour of 2,5-diphenyl-1,3,4-thiadiazole (45) lies somewhere between that of 2,5-diphenyloxazole (30), in which the isomer ratio is almost constant irrespective of the nitrating medium, and that of 2,5-diphenyl-1,3,4-oxadiazole (35), in which the ratios vary considerably. It was considered possible that this might be due to differences in pK_a's of the three compounds; Sagar[65] had already calculated the pK_a of 2,5-diphenyl-1,3,4-oxadiazole (35) to be -1.20 and -2.45, but the pK_a's of the other two compounds have not been previously measured.

2.3 Determination of pK_a's of 2,5-diphenyl-1,3,4-thiadiazole and 2,5-diphenyloxazole.

The determination of ionisation constant by ultraviolet spectrophotometry depends upon the direct determination of the ratio of molecular species (neutral molecule) to ionised species. For this purpose, the spectrum of the molecular species is obtained in a solution whose pH is so chosen that the compound to be measured is present wholly as unprotonated species. This spectrum is compared with that of the pure ionised species similarly obtained at another suitable pH.

The wavelength chosen for pK_a determination is the one at which the greatest difference between the absorbance of the two species is observed. This is termed the analytical wavelength.

Accordingly the absorbance of the two compounds (30 and 45) under consideration was taken in glacial acetic acid (d 1.05) and glacial acetic acid and concentrated sulphuric acid (d 1.84) mixture (63.5/35.5 w/w). The wavelength selected on the basis of their absorbance was 340 nm. By measuring absorbance at various acid concentrations intermediate between those at which the spectra of the two species were obtained, the ratio of ionised to molecular species can be calculated. It is possible because a series of two-component mixtures is formed in which the ratio of the two species depends solely upon the H_o at which the solution is optically measured. The observed optical density d, at the analytical wavelength, will be due to the sum of the optical densities of the ionised species d_I and molecular species d_M;

$$\text{i.e.} \qquad d = d_I + d_M$$

The optical density of either component is related to its molar concentration C by a general expression

$$d = \varepsilon . l . c$$

where ε is the molar extinction coefficient of the particular species

and l is the optical path-length of the cell.

The pK_a of a base is represented by the relationship

$$pK_a = pH + \log (\varepsilon - \varepsilon_M)/(\varepsilon_I - \varepsilon)$$

where ε_I is the extinction coefficient of the protonated base (ion) at the analytical wavelength, ε_M is the extinction coefficient of the unprotonated molecule at the analytical wavelength and ε is the extinction coefficient of the mixture of ions and molecules at the same wavelength.

If the same cell path-length is used for all the measurements and concentration of the compound kept constant for all measurements then optical density becomes directly proportional to the molar extinction coefficient;

$$\text{i.e.} \quad d \propto \varepsilon$$

At high acidities H_o is a more accurate measure of acidity than pH; the above equation for pK_a can be rewritten as

$$pK_a = H_o + \log (d - d_M)/(d_I - d).$$

The spectroscopic method, therefore, involves the determination of the relative amounts of the free base and ionised species, when the base is dissolved in a series of solutions of accurately known acid strength (H_o).

The H_o values for the mixture of concentrated sulphuric acid and acetic acid have been determined by Hall and Spengeman[87] and lie between +0.09 to -6.03. The H_o values for pure acetic acid

(containing no sulphuric acid) was obtained by graphical extrapolation of Hall and Spengeman's[87] data. The results of these determinations are presented in the graphical form (figure 3 and 4).

The pK_a of the base is taken to be the H_o at half protonation with this graphical approach (the H_o value halfway between the horizontal portions of the curve). The two results are as under:-

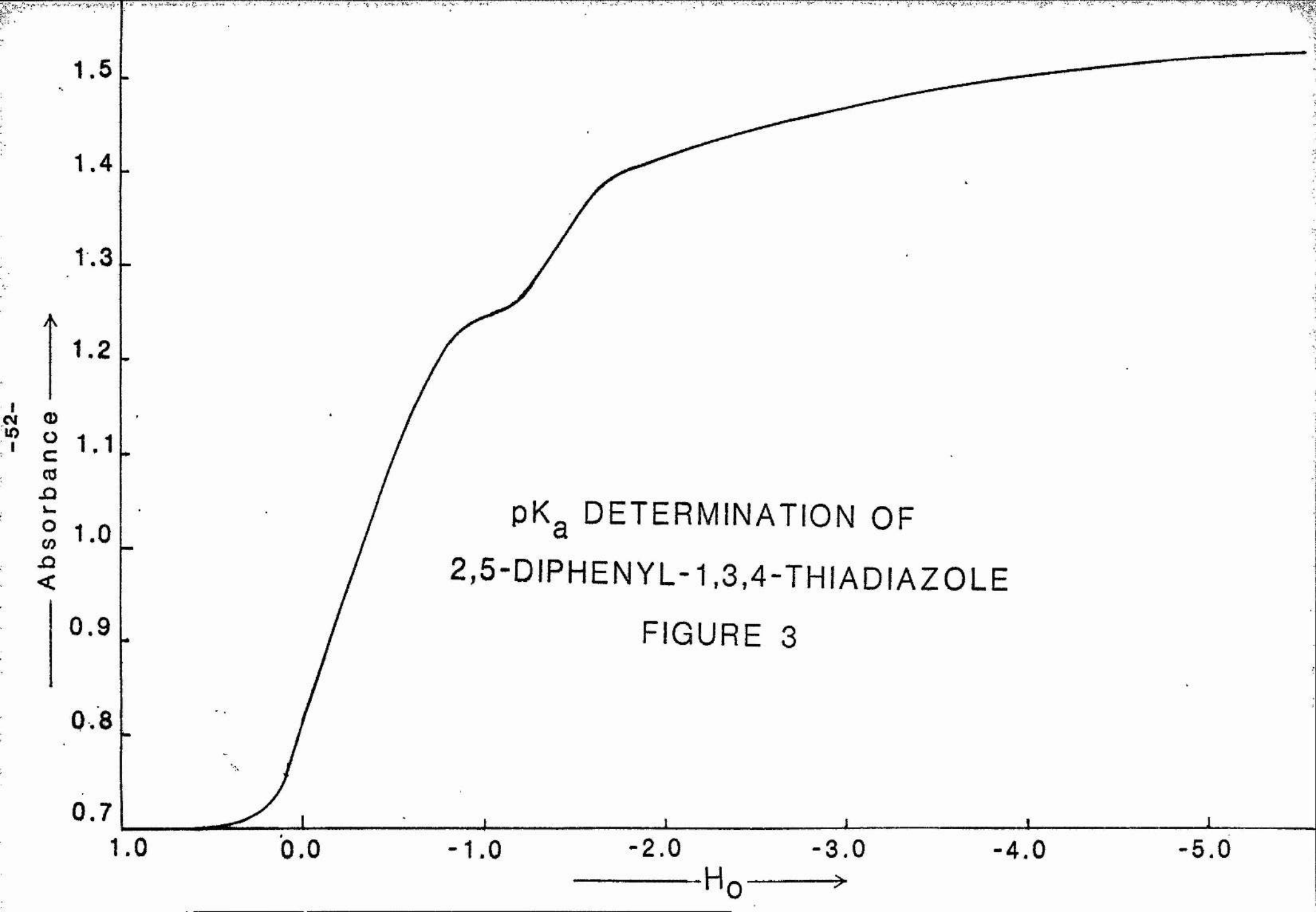
i) 2,5-diphenyl-1,3,4-thiadiazole -0.25, -1.34;

ii) 2,5-diphenyloxazole +0.50.

2.3.1 Comments on the basicity results

On close observation of figure 3 and 4 it becomes obvious that as the acid strength increases so does the density in a stepwise fashion. Each step must correspond to a change in the species present.

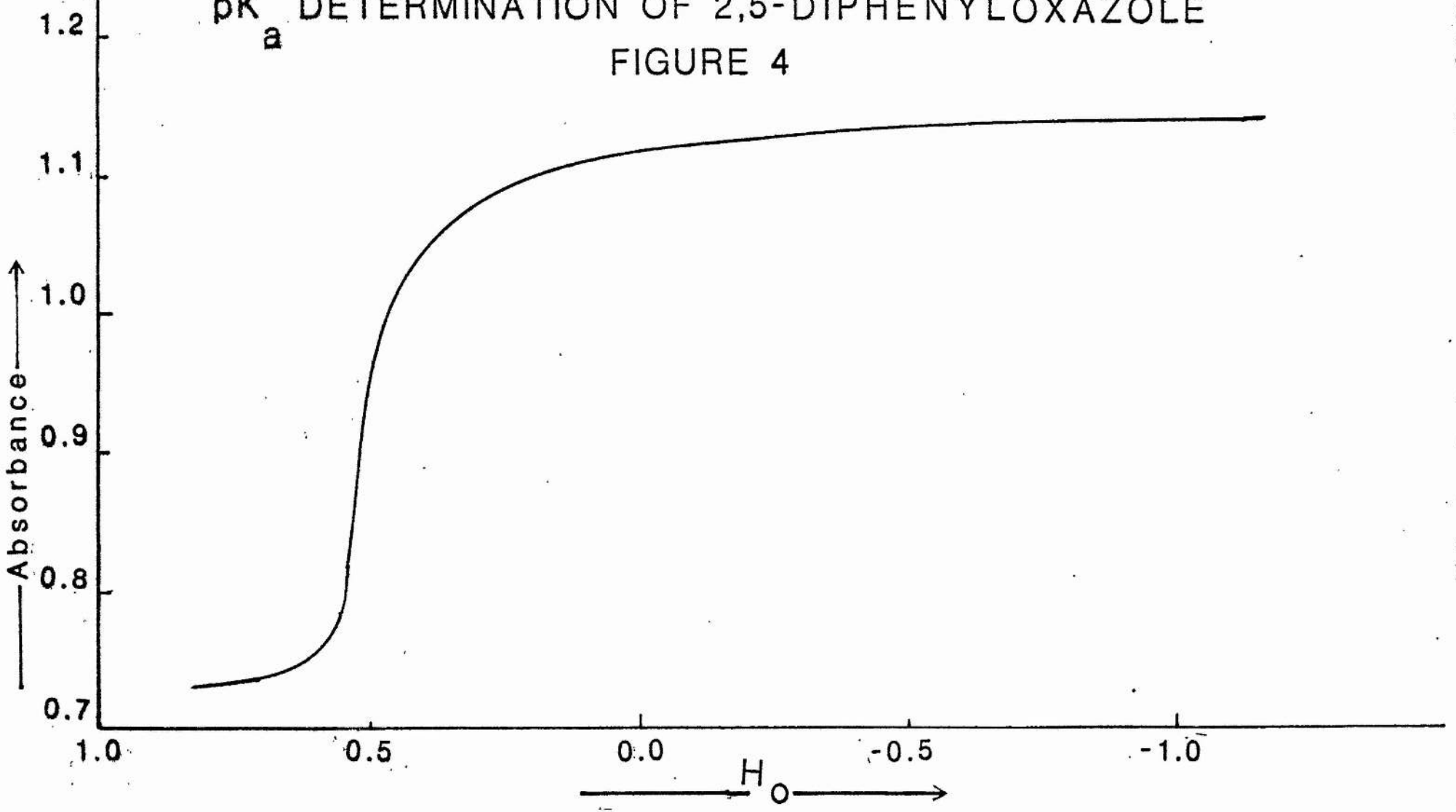
So far as the oxazole is concerned (figure 4) the results seems to to be fairly simple to interpret, there being only one centre where protonation can take place. One step observed (at half protonation, pK_a) in the curve could be attributed to a protonation of the nitrogen atom and since there does not seem to be any evidence from experimental data, that another big change



pK_a DETERMINATION OF
2,5-DIPHENYL-1,3,4-THIADIAZOLE
FIGURE 3

pK_a DETERMINATION OF 2,5-DIPHENYLOXAZOLE

FIGURE 4



in absorbance (another step) has taken place after the first change, it could be safely assumed that genuine protonation has taken place. (The pK_a of oxazole is 0.80)[88].

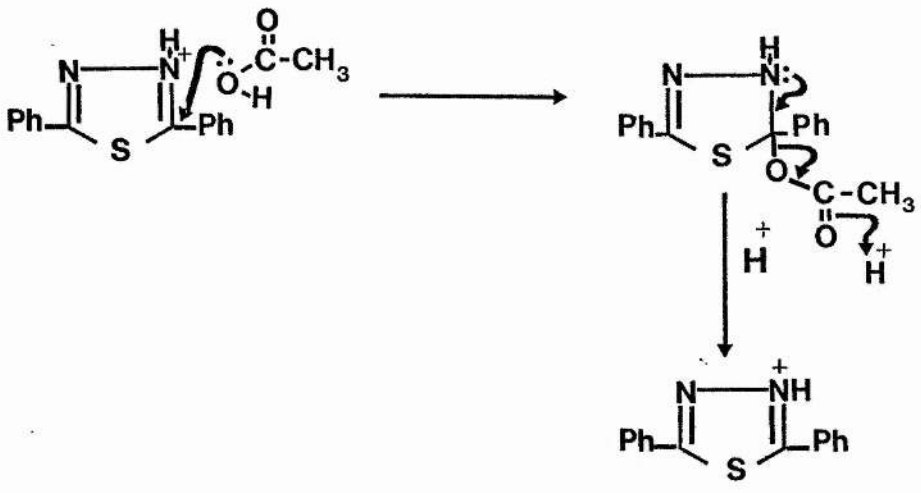
The protonation behaviour of 2,5-diphenyl-1,3,4-thiadiazole in sulphuric acid and acetic acid is similar to that of protonation of 2,5-diphenyl-1,3,4-oxadiazole[65]. Either the first step is the monoprotonation of the compound and the second step is the diprotonation of the compound (45), or alternatively the first step is the formation of an intermediate and the second step is the ultimate formation of a monoprotonated molecule.

The results for 2,5-diphenyl-1,3,4-thiadiazole (45) are similarly not straightforward as there are two adjacent nitrogens, either of which could be individually protonated after each another; this could correspond to the two steps in the absorption curve of the compound. As in the case of the oxadiazole, however, the difference observed in the pK_a's of these two steps is small as compared to the difference expected (figure 3) from such close proximity of two positive centres. Similarly the observed difference in pK_a's expected, if one of the nitrogens is protonated and the other protonation occurs at sulphur is still small.

From the foregoing the following can be postulated:-

In the first step the elements of acetic acid are added

across one of the nitrogen-carbon bonds (Scheme 25). The acetoxy-group is eliminated in the second step to give a protonated thiadiazole. This is similar to what has been proposed for the oxadiazole[65,66].



Scheme 25

A lot of work still has to be done before anything definite can be said about the foregoing possibility.

2.4 Interpretation of the results of the nitration Of 2,5-diphenyl-1,3,4-oxadiazole and -thiadiazole

On the basis of the nitration results in section 2.3, any mechanism proposed must be capable of explaining the following experimental results.

a) Unlike the case of 2,5-diphenyloxazole (30) there are appreciable variations in the isomer ratios obtained for the nitration of 2,5-diphenyl-1,3,4-thiadiazole (45) under

different reaction conditions but not to such an extent as in the case of 2,5-diphenyl-1,3,4-oxadiazole (35). The general behaviour pattern of (45) lies somewhere between the oxazole (30) and the oxadiazole (35).

b) Nitration of the phenyl ring is effectively irreversible [This conclusion is drawn from the three nitrations of the mono-nitro-isomers of oxadiazole and thiadiazole (tables 3-5 and 8-10) when in each case only three products were obtained].

c) Changing from fuming nitric acid to nitric acid in sulphuric acid and from there to nitronium tetrafluoroborate there is a meta-effect in the nitration of 2,5-diphenyl-1,3,4-thiadiazole (45) but again not so pronounced an effect as in the case of 2,5-diphenyl-oxadiazole (35).

d) 2,5-Diphenyl-1,3,4-thiadiazole (45) is slightly more basic as compared to 2,5-diphenyl-1,3,4-oxadiazole (35).

e) In nitration with nitronium tetrafluoroborate there is no similar increase in ortho-nitro-isomer in the case of thiadiazole (45) like the oxadiazole (35).

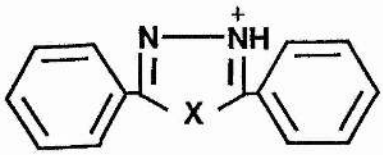
The pK_a values of 2,5-diphenyl-1,3,4-thiadiazole are -0.25 and -1.34 (figure 3) and the pK_a values of oxadiazole (35) are -1.20 and -2.45, the area wherein the species can undergo

electrophilic substitution either as free base or as a conjugate acid depending on the acid strength of the medium. It is , therefore, reasonable to assume that the variation in isomer ratio obtained in both cases may be accounted for in part at least by a variation in species or a variation in mixture of species undergoing nitration under different reaction condition.

The overall results of the nitration could be explained if the type(s) of species undergoing nitration could be identified and the directive effect they can have on the incoming electrophiles can be determined.

a) In the case of the neutral species the effect of the heterocyclic ring on the phenyl ring appears to be slightly deactivating as compared to benzene, but due to this feeble effect no definite directive influence appears likely and nitration in all the three positions may therefore take place (ortho-, meta-, para-).

b) Because the atoms in the hetero-ring are electron-rich (six π-electrons are distributed over five atoms) therefore as compared to a six-membered ring a protonated five-membered ring will not be as electron-withdrawing as a protonated six-membered ring but it can still have a residual effect (-I) on the attached phenyl ring through sigma bonds, and if the rings are coplanar, through conjugation of π-bonds (mesomeric effect).



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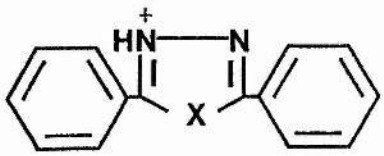
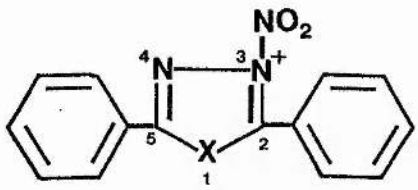


(56)

It must be remembered, of course, that the protonation of the heterocycle on nitrogen makes the phenyl groups non-equivalent, and the nitration in these two rings may therefore be different both in rate of reaction and in isomer ratio. The ring nearest to the protonated nitrogen probably will be less reactive due to the static and negative inductive effects of the 'positive pole'[70,71] even if we ignore the +M effect. In the second nitration step, the starting material (mono-nitro compound) may be protonated at either of the two (now non-equivalent) nitrogens, and each of these two species may give different isomer ratios.

c) There is yet another possibility. Either of the nitrogens could be quaternised, by the nitronium ion (NO_2^+). If N-3 in the structure (57) is quaternised, it is reasonable to expect the 5-phenyl group to be more reactive, since it is further from the positively charged centre; in the second nitration step, the 2-phenyl substituent would be involved, and intramolecular transfer of the nitro-group (cf.p.33) may then become important. This idea is supported by the results in the oxadiazole series (Tables 3-7,p.34) in

which there is a large ortho-effect in the second nitration step.



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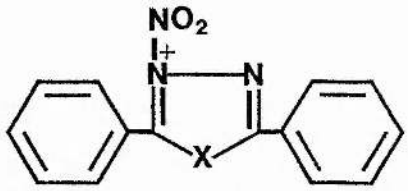


(58)

The variation in isomer ratios being large in the case of the oxadiazole (35) as compared to the thiadiazole (45) could be accounted for by considering the difference in pK_a's and by presuming that the ratios of different species undergoing nitration in both cases may be different.

The oxazole (30) and the benzimidazole (29) show little variation in isomer ratios when the conditions are changed; since these are more basic than the oxadiazole and thiadiazole, it may be presumed that both are nitrated as conjugate acids.

2.4.1 Nitration in Nitric Acid and Sulphuric Acid

It has been proposed that 2,5-diphenyl-1,3,4-oxadiazole[65,66](35) in nitric acid and sulphuric acid mixture undergoes nitration as its conjugate acid. By analogy, we propose that 2,5-diphenyl-1,3,4-thiadiazole (45) also undergoes nitration as a conjugate acid in this medium, especially since it is more basic than (35). It is further

assumed that mono-protonation takes place on one of the heterocyclic nitrogens and for the duration of the nitration the site of protonation does not change.

Protonation of both the hetero-atoms at the same time is less likely as the sites of protonation are adjacent and stabilisation of both positive charges in such close proximity is difficult.

In the second stage of nitration of both (35) and (45)(Tables 3-5 and 8-10) in nitric acid and sulphuric acid there is a considerable increase of meta-nitration as compared to nitration in nitric acid alone.

The difference in isomer ratios between the first nitration and the second nitration may be due to the fact that the two different protonated species may be undergoing nitration. In the second stage of nitration the increase in meta-substitution could be accounted for by the major site of protonation being nearer to the phenyl ring undergoing nitration and thus exerting a 'positive pole' effect[70,71].

The foregoing arguments based on the results of nitration of (45) are consistent with the idea that the site of protonation does not change during nitration and the possibility that two or more species are involved in the second nitration cannot be ruled out.

2.4.2 Nitration of 2,5-diphenyl-1,3,4-thiadiazole in nitric acid

Unlike 2,5-diphenyl-1,3,4-oxadiazole (35), when 2,5-diphenyl-1,3,4-thiadiazole (45) is nitrated in fuming nitric acid alone the nitration products are not very significantly different from those obtained in sulphuric acid and nitric acid. The only difference is that there is a slight increase in para-nitro-isomers and a slight decrease in meta-nitro-isomers but this effect is not nearly as pronounced as is the case with oxadiazole (35).

A tentative explanation for the difference in nitration behaviour between the oxadiazole (35) and the thiadiazole (45) may be as follows (although it still has to be proved).

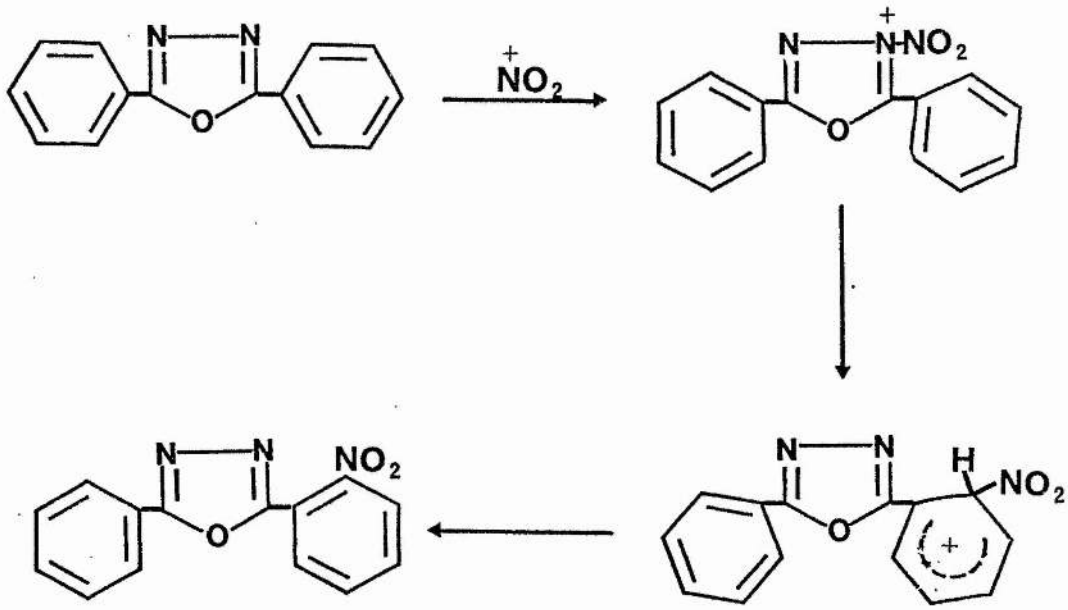
Since the thiadiazole is somewhat more basic than the oxadiazole, it may be protonated to a greater extent than the oxadiazole in the fuming nitric acid. Alternatively it may be quaternised by NO_2^+ to a greater extent. There would thus be less difference in the species present between the different nitrating media than is the case with the oxadiazole, and therefore less variation in isomer ratios.

2.4.3 Nitration in sulpholane with nitronium tetrafluoroborate

Results obtained by the nitration of 2,5-diphenyl-

1,3,4-thiadiazole (45) in the non-acidic medium using nitronium tetrafluoroborate show a similar trend to its oxadiazole analogue, i.e.the enhancement of meta-nitro-isomer. But the similarity ends there; increase in the proportion of ortho-nitro-isomer,especially in the second nitration step, does not take place in the case of (45).

As has been explained above, this ortho-substitution of (35) has been attributed to an intramolecular transfer of NO_2^+ from the heteroatom to the adjacent ortho-position of the phenyl ring (Scheme 26).



Scheme 26

In the case of the thiadiazole it is proposed that the increased basicity may indicate a corresponding increase in

nucleophilicity of the heteroatoms, and that the NO_2^+ group may therefore be less easily detachable from the heteroatoms. This would require that most of the nitration process is intermolecular and would give isomer ratios similar to those in strongly acid conditions (section 2.4.1).

It is also possible of course, that the difference between the oxadiazole and thiadiazole series may be the result of the different geometry of the heterocyclic rings; the phenyl-heterocycle C-C bonds are much more nearly linear in the thiadiazole (because of the larger sulphur atom), and it may be that, in the oxadiazole, the geometry is particularly favourable for the intramolecular reaction.

A lot of experimental work has to be done in this field before definite conclusions could be derived in these substitution reactions.

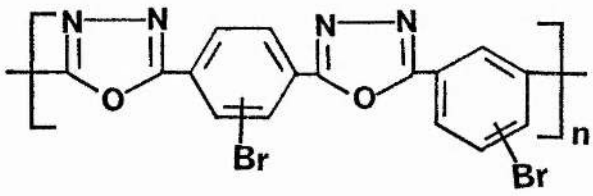
Chapter 3

Bromination : Results and Discussion

3.1 Bromination of 2-phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole

Poly(bromophenylene-1,3,4-oxadiazoles) (59) compared with their unbrominated analogues, have enhanced flame resistance properties[91] and there is to some extent an overall improvement of their other properties such as tearing strength.

The bromine in these polymers is introduced either using bromo-dicarboxylic acid monomers or by bromination of the polymers using bromine in oleum[6,24,91].



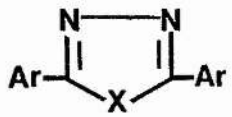
(59)

Bromination of the low molecular weight analogues such as (60), carried out in oleum, results in polybromination[65] and each phenyl ring is brominated with up to five bromines according to the number of substituents already present and the quantity of

bromine used.

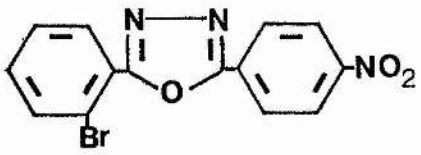
Polymers derived from mixtures of monomers or by modification (e.g. bromination) of another polymer will not be homogeneous and their properties will differ from batch to batch. So the number of bromine atoms present and their orientation in each phenyl ring of the molecule becomes important. A study was undertaken to investigate these parameters and to determine if some control could be exercised over the number of bromine atoms entering each phenyl ring and their orientation with respect to each other.

Monobromination of each phenyl ring of 2,5-diphenyl-1,3,4-oxadiazole (35) gives six possible isomers, and dibromination of each phenyl ring gives twenty-one possible isomers. In order to keep the number of bromination products within manageable limits, one phenyl ring can be deactivated towards further electrophilic substitution under the conditions employed by the introduction of a nitro-group. Even then there are three isomers of monobromination (61), (62), and (63), and six possible dibromo-isomers (64)-(69).

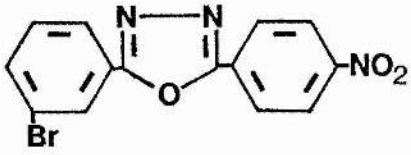


X = O,S

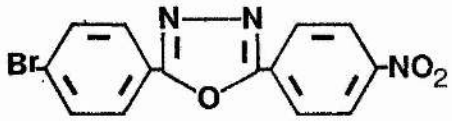
(60)



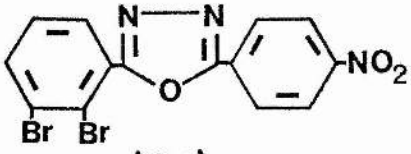
(61)



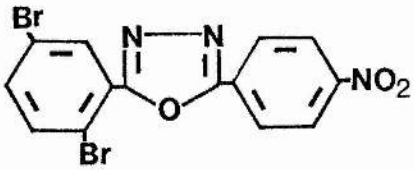
(62)



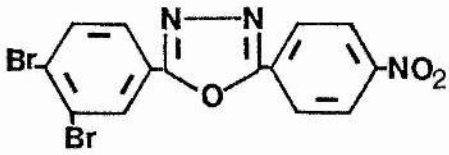
(63)



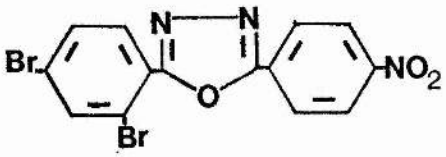
(64)



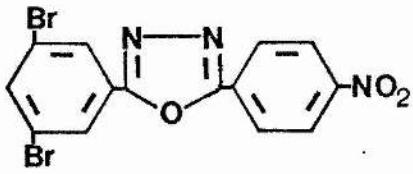
(65)



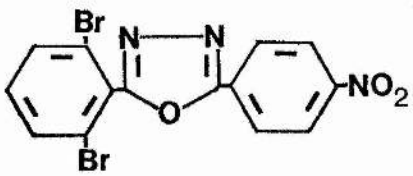
(66)



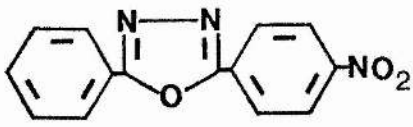
(67)



(68)



(69)



(44)

From the previous work[65], the relative lack of reactivity of the phenyl ring in (44) towards electrophilic substitution was known and various brominating techniques were tried to brominate (44), but the method which gave the most encouraging results was one of Derbyshire and Waters'[92] methods for bromination of unreactive aromatic rings, using bromine and potassium bromate in sulphuric acid and acetic acid.

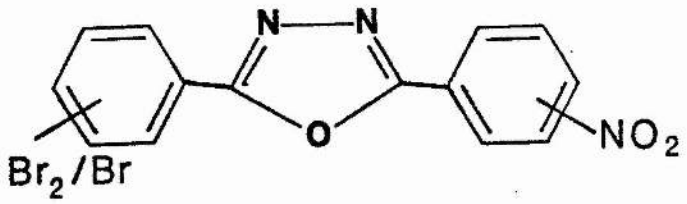
First bromination of (44) was carried out in the manner outlined by Derbyshire and Waters[92] using a 1:1:2 ratio of oxadiazole (44) to bromine to potassium bromate.

The separation of products in the nitration experiments used a 'normal phase' h.p.l.c. column (silica). In this case however, separation using a normal phase column could not be effected, because of the similiarity in the polarity of the products. A 'reverse phase' column with a high percentage (15%) of ODS was however able to effect separation of the various isomers.

Instead of three peaks expected on monobromination of (44) seven peaks were obtained (figure 5 and table 12 line 2). It was assumed that partial dibromination had also taken place.

Compound (44) was brominated once more using 2:1:2 ratio of oxadiazole (44) to bromine to potassium bromate. We again

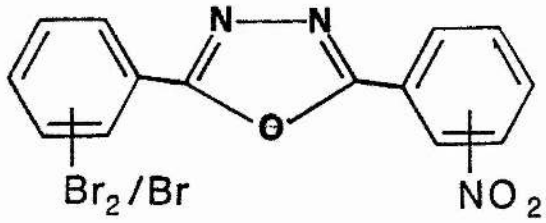
LIQUID CHROMATOGRAM OF



COMPOUNDS

FIGURE 5

LIQUID CHROMATOGRAM OF



COMPOUNDS

FIGURE 6

TABLE 12

Products of bromination of 2-p-nitrophenyl-5-phenyl- (or -bromophenyl-) -1,3,4-thiadiazole

Starting Compound	Br_2 (mmole)	$KBrO_3$ (mmole)	Composition (mole %) of product * mixture (h.p.l.c.)							Starting material accounted for %
			5-Ph	Monobromo-			Dibromo-			
			44	o- 61	m- 62	p- 63	2,3- 64	2,5- 65	3,4- 66	
(44) (5 mmole)	2.5	5	35	16	14	26	1	6	2	62
(44) (5 mmole)	5	10	0.5	5	7	31	9	29	19	55
(61) (1.9 mmole)	1.25	2.75	-	23	-	-	26	51	-	62
(62) (1.9 mmole)	1.25	2.75	-	-	25	-	9	41	25	71
(63) (1.9 mmole)	1.25	2.75	-	-	-	8	-	-	90	74 **

* Each h.p.l.c. peak area, on which the percentage composition is based, is the mean of at least three determinations (cf. Experimental); the deviation from this mean value is very small (3%).

**ca. 2% tribromo-compound also formed.

obtained the same seven peaks but in different proportions (figure 6).

3.2 Analysis of Bromination Products

In order to evaluate the results of bromination all the nine compounds listed earlier (61-69) were synthesised. With the help of these compounds, the various bromination products were identified and the mixtures quantitatively analysed.

The first peak in both cases was unreacted starting material (44) and the next three peaks correspond to the monobromo-isomers (61), (62), and (63) respectively. The next two peaks overlap slightly; these two were identified as the 2,3- and 2,5-dibromoisomers (64) and (65) respectively and the seventh peak was identified as the 3,4-dibromo-compound (66). The other three dibromo-isomers (67), (68), and (69) were not detected in the bromination products.

In order to assess the above-mentioned results more thoroughly, bromination of the mono-bromo-compounds (61), (62), and (63) was undertaken with a 34:20:44 ratio of oxadiazole (44) to bromine to potassium bromate (i.e. a moderate excess of brominating agent). The results obtained are summarised in table 12. The general characteristics of the monobromo and dibromo compounds and their hydrazide precursors are summarised in tables 13 and 14.

TABLE 13

5-(Bromo- and Dibromophenyl)-2-*p*-nitrophenyl-1,3,4-oxadiazoles

Compound No.	Position of bromine(s)	Yield (%)	M.p. (recryst. solvent)	Found, % C	H	N	H.p.l.c. 'response factor' at 290 nm
(a) Monobromo-compounds*							
61	*o*-	87	184-186 (DMF/AcOH)	48.45	2.3	12.1	1.00
62	*m*-	74	202-203 (DMF/AcOH)	48.3	2.3	12.0	1.39
63	*p*-	86	248-250 (DMF/AcOH)	48.8	2.3	12.4	1.04
(b) Dibromo-compounds†							
64	2,3-	75	226-228 (AcOH)	39.3	1.7	9.8	1.20
67	2,4-	65	194-196 (AcOH)	39.3	1.6	9.8	
65	2,5-	66	239-240 (AcOH)	39.9	1.6	9.9	1.01
69	2,6-	50	270-272 (AcOH/H_2O)	39.35	1.7	9.85	
66	3,4-	42	246-248 (AcOH)	39.2	1.7	9.8	1.06
68	3,5-	49	226-228 (DMF/AcOH)	39.5	1.7	9.8	

*$C_{14}H_8BrN_3O_3$ requires C, 48·6; H, 2.3; N, 12.1%

†$C_{14}H_7Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%

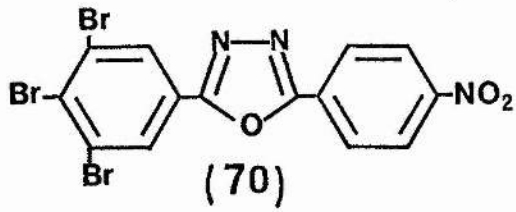
TABLE 14

1-(Bromo- and Dibromobenzoyl)-2-(*p*-nitrobenzoyl)hydrazines

	Position of bromine(s)	Yield (%)	M.p., °C (recryst. solvent)	Found, % C	H	N
(a) Monobromo-compounds*						
	o-	77	250-252 (AcOH)	46.4	2.8	11.55
	m-	79	213-215 (AcOH)	46.45	2.8	11.6
	p-	63	292-294 (DMF)	46.0	2.7	11.6
(b) Dibromo-compounds†						
	2,3-	67	258-260 (AcOH)	37.7	2.1	9.4
	2,4-	70	254-256 (AcOH)	37.6	2.1	9.35
	2,5-	70	264-265 (AcOH/H_2O)	37.8	2.0	9.3
	2,6-	65	314-316 (AcOH/H_2O)	37.5	2.0	9.4
	3,4-	63	266-268 (AcOH)	38.3	2.0	9.4
	3,5-	48	256-258(DMF/AcOH)	37.55	2.1	9.2

*$C_{14}H_{10}BrN_3O_4$ requires C, 46·2; H, 2·8; N, 11.5%.

†$C_{14}H_9Br_2N_3O_4$ requires C, 37,95; H, 2·05; N, 9.5%.



(70)

Close observation of table 12 shows that (61) on bromination gave two products, 2,3-dibromo- (64) (ortho-oriented) and 2,5-dibromo- (65) (para-oriented). Bromination of (62) gave three products (64), (65), and (66); (64) and (66) having bromines ortho- to one another and (65) being para-oriented. Bromination of (63) gave only one dibromo-product (66) which is ortho- oriented but there was another product (less than 2 %) which is a tribromo-isomer believed to be 2-(3,4,5-tribromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole (70), but we could not positively identify it because of its very low solubility in the h.p.l.c. solvent system.

3.3 Interpretation of Bromination Results

There are no proper studies in the literature of the bromination (at the phenyl rings) of 2,5-diphenyl-1,3,4-oxadiazole (35). There is however one bromination study carried out by Sagar[65]. There have also been no rigorous studies carried out of bromination of other phenyl heterocycles, unlike the corresponding nitration studies.

The interpretation of the results must take into account the following experimental facts:-

i) Mono-bromination of the phenyl ring takes place at all the three positions (ortho-, meta-, and para-).

ii) The second bromination occurs even where there is still starting material left.

iii) The second bromination is controlled by the first bromine in accordance with the well-established principle that bromine is ortho-/para- directing in electrophilic aromatic substitution.

It is obvious from table 12 that the bromination products isolated in each case account for less than 75 % of the starting material. Effort was made to recover any product still present in the acidic reaction medium by neutralising it, but nothing significant was recovered. We believe that the remainder of the oxadiazoles are consumed in side reactions which compete with (or follow) bromination. This is consistent with the small amount of several polar by-products which were detected by h.p.l.c. during analysis of the oxadiazole mixtures. The nature of these side reactions is uncertain, although oxidation of benzene rings has previously been observed[93] during bromination of deactivated aromatic compounds with potassium bromate and sulphuric acid, and oxidative or hydrolytic ring-opening of the heterocycles are also possible.

As stated earlier, the nitration studies of (44) carried out by Sagar, Smith, et al.[65,66], in various nitrating media show that in every case ortho-, meta-, and para- nitration of the phenyl

rings all occur to an appreciable extent.

In fuming nitric acid the ratio of ortho-, meta-, and para-nitro-isomers obtained[65,66] on nitration of (44) was 34: 23: 43 (Table 5). The first line of table 12 indicates that monobromination of compound (44) similarly gives all the three possible isomers ortho-, meta-, and para- to a reasonable extent and if allowance is made for the 9% of dibromo-compounds, the ratio comes to 28.5:28.5:43. This compares well with the nitration results from (44). We can reasonably assume from the foregoing that the same type of specie(s) is/are undergoing substitution in each case.

Derbyshire and Waters[92] have put forward the idea that the brominating species with molecular bromine and potassium bromate in sulphuric acid and acetic acid is either (Br^+) or $(H_2OBr)^+$ which is a conjugate acid of the very weak base HOBr, as shown below.

$$Br_2 + H_2O \rightleftharpoons HOBr + HBr$$

$$H^+ + HOBr \rightleftharpoons H_2O + Br^+$$

$$5HBr + HBrO_3 \longrightarrow 3H_2O + 3\ Br_2$$

or alternatively

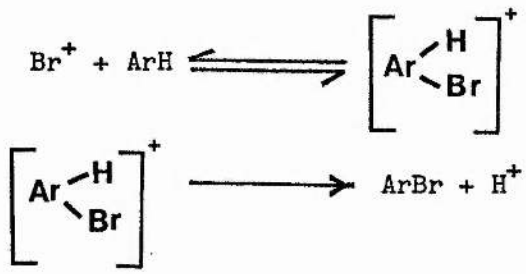
$$H^+ + HOBr \rightleftharpoons (H_2OBr)^+$$

The more recent work of Harrison, Pellegrini and Selwitz[93] suggested that the quantity of bromine may not be relevant and the function of the bromate is to remove bromide ion (Br^-) from the equilibrium and to generate hypobromous acid which in the presence of sulphuric acid is a powerful brominating agent.

$$Br_2 + H_2O \rightleftharpoons H^+ + Br^- + HOBr$$

$$5Br^- + 6H^+ + BrO_3^- \longrightarrow 3Br_2 + 3H_2O$$

The second assumption we make is that bromination, like nitration, is not reversible. (Results obtained on bromination of the mono-bromo- isomers (61-63) could be used as support for this argument). The kinetics of bromination (Scheme 27)[94] indicate that the first step, the formation of a charged intermediate, is the rate determining step for this mechanism. The second step, the loss of a proton, is very fast and therefore kinetically insignificant.

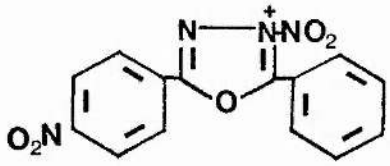


Scheme 27

In these bromination experiments (table 12), only three of the six isomers, *viz.* (64), (65), and (66), were detected by

h.p.l.c. The presence of other three, *viz.* (67), (68), and (69), was not detected (detection limit <0.1%). In every case the second bromination of the phenyl ring takes place only *ortho*- or *para*- to the bromine already present. It is safe to assume from these results that any stabilising influence/effect of the oxadiazole ring on the positively charged transition states for these electrophilic brominations is feeble compared with mesomeric stabilisation by the bromine atom.

In the nitration of compound (44) using nitronium tetrafluoroborate[65,66] the usually high proportion (50 %) of *ortho*-nitration has been attributed to an *N*-nitro-1,3,4-oxadiazolium cation (71)



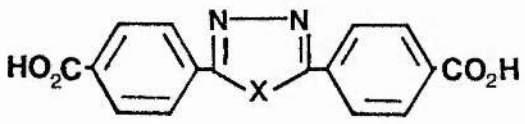
and subsequently intramolecular transfer of (NO_2^+) to the adjacent carbon atom. This type of intramolecular process does not seem to take place in the bromination of (44), if the *N*-bromo-oxadiazolium cation is involved at all, it does not lead to an especially high yield of *ortho*-brominated products. The isomer ratios obtained in the second bromination may be rationalised simply in terms of the different degrees of steric hindrance at the ring carbons of the monobromo-compounds (61-63).

Chapter 4

Synthesis of (1,3,4-oxadiazole-2,5-diyl)-dibenzoic acids and their thiadiazole analogues

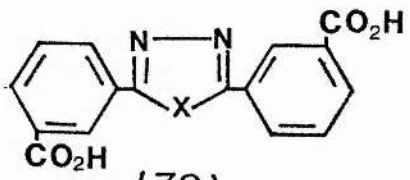
4.1 Patent Methods of Synthesis

The use of p,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoic acid (72) and its meta-substituted analogue (73) and their thiadiazole analogues is on the increase as their importance is being realised. ICI Petrochemicals and Plastics Division was interested in a simple and cheaper method of synthesis of these compounds than those previously available. They brought this problem to our attention and donated some chemicals for this project, for which we are thankful to them.



(72)

a: X = O
b: X = S



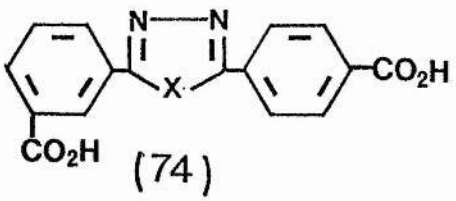
(73)

Symmetrical dicarboxylic acids of the type (72) and (73) and their simple derivatives, e.g. acid chlorides and hydrazides have been used as starting materials for several polymerisation studies[18,23,95-100] and some of their esters have been used as additives[19-21,101,102] for different polymers to modify or

improve their properties.

There are numerous procedures for their synthesis and many of the synthetic routes have been published in the form of patents[17-22,95-105].

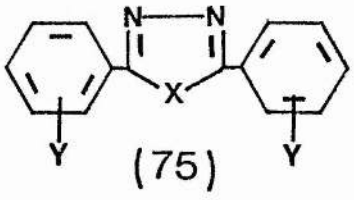
The object of the project was not only to find an efficient and simple method for the synthesis of the symmetrical dibasic acids (72a, 73a, 72b, 73b) but also to produce the mixed (unsymmetrical) acids(74a and 74b) cheaply and in a high state of purity.



(74)

a : X = O

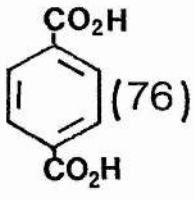
b : X = S



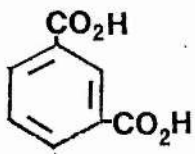
(75)

Y = m-CO_2H or p-CO_2H

One of the two favoured literature routes for the synthesis of (72a) or (73a) starts from terephthalic acid (76) or isophthalic acid (77).

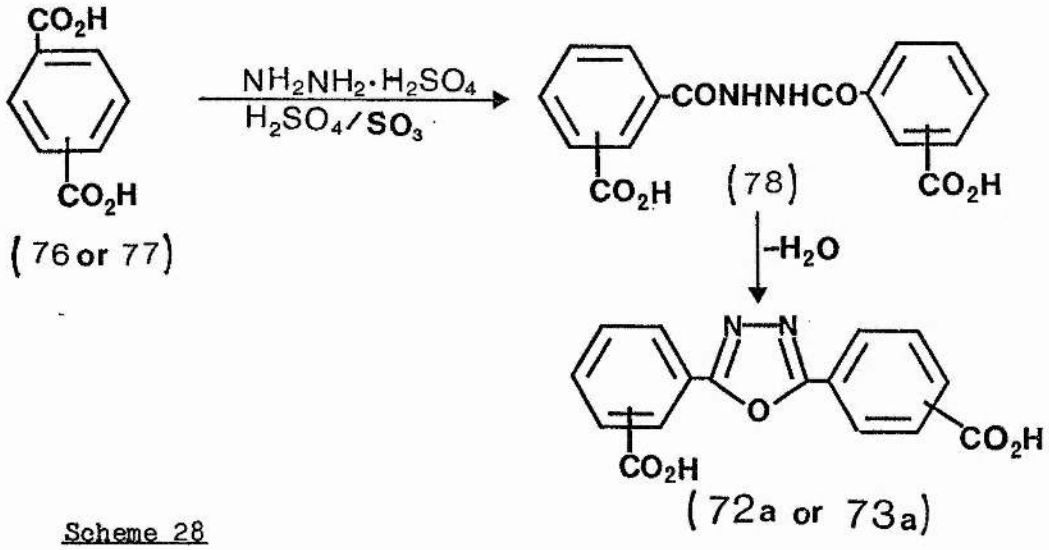


(76)



(77)

and is conveniently referred to as the 'oleum method' (Scheme 28).

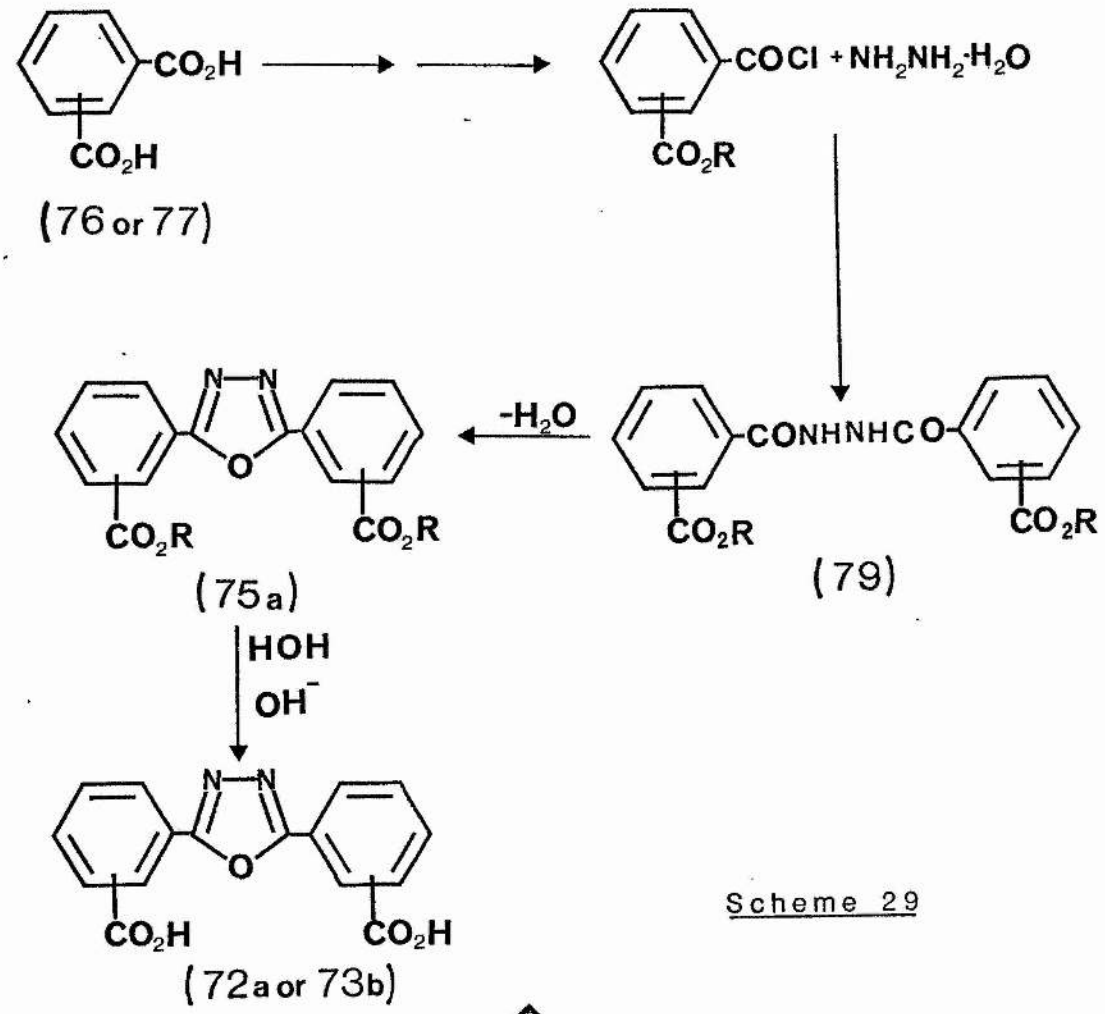


Scheme 28

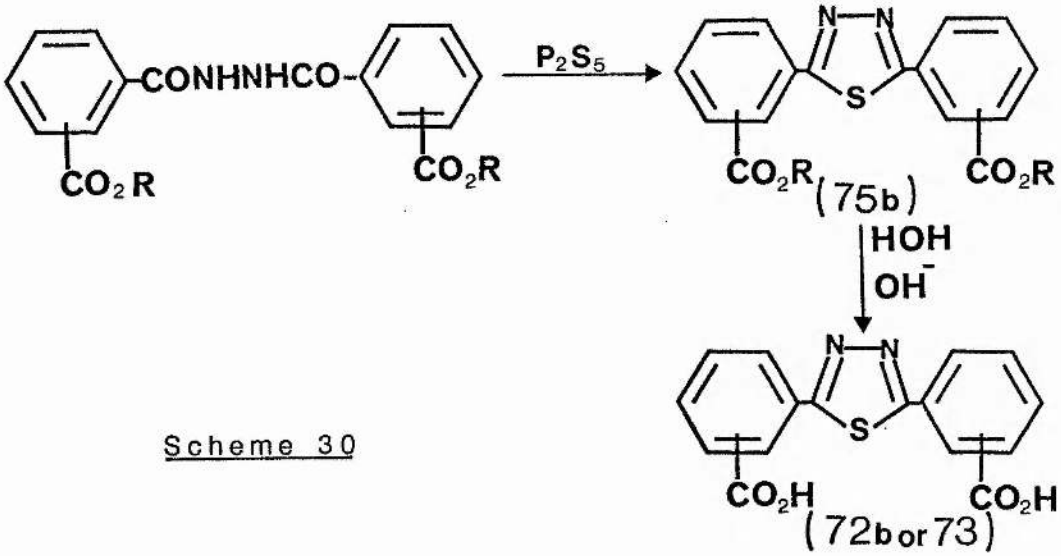
The method consists of adding slightly more than 2 mole equivalents of (76) or (77) to one mole equivalent of hydrazine sulphate in oleum containing 25% sulphur trioxide. This theoretically results in the formation of the disubstituted hydrazine (78), which then loses one molecule of water to give the required oxadiazole (72a) or (73a).

So when we were asked to look into the possibility of producing these monomers, naturally we tried this method first for the production of the symmetrical oxadiazole isomers.

The second literature method[18-22] consists of reacting a suitably protected acid chloride of (76) or (77) with hydrazine hydrate in tetrahydrofuran. The aroylhydrazine (79) produced is cyclised in refluxing phosphorus oxychloride (Scheme 29)[18-22] and thus gives oxadiazole (72a) or (73a) (Chapter 1, Scheme 3a)[34,35].



Scheme 29



Scheme 30

The second method, unlike the first, could in theory be modified to produce symmetrical thiadiazoles by substitution of phosphorus pentasulphide for phosphorus oxychloride (Scheme 30)[18].

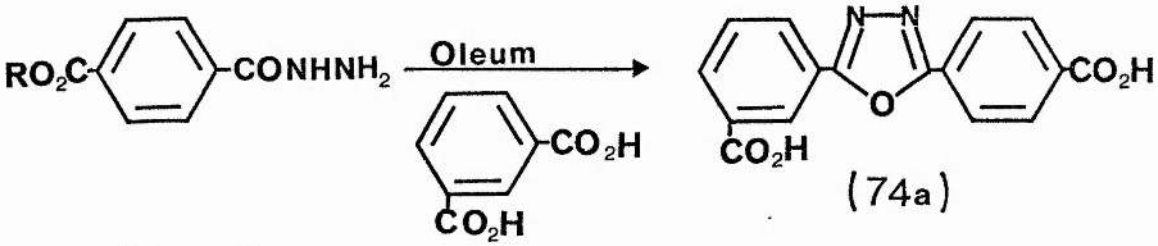
In practice the 'oleum method' on work up gave quantitative yields but 50% of the product appeared to be a mixture of high melting polymer and the starting acid. This is not really surprising, since the standard method for the production of poly(phenylene-1,3,4-oxadiazoles) involves the reaction in oleum of the same acid and hydrazine sulphate (in equimolar amounts).

Since purity of these compounds is of paramount importance for polymerisation purposes, so it was thought that a suitable method for the purification of these products might be an answer to our problem. The purification of the acids (72a) and (73a) was effected as follows:-

The crude product was dissolved as far as possible in a solution of sodium carbonate , filtered to remove part of the insoluble polymer, and the acidic material, reprecipitated by addition of hydrochloric acid. The precipitate was in a very fine state and centrifuging was necessary to effect separation. The product obtained at this stage still contained some polymer and the starting material (76 or 77) in addition to (72a) and (73a).

Further purification was effected by preparing the bis-acid chlorides of the acidic components by heating the mixture with phosphorus pentachloride on a Bunsen flame. The bis-acid chloride mixture so obtained was extracted with hot petroleum (b.p. 40-60); the bis-acid chloride of either (76) or (77), being soluble in hot petroleum, was thus removed. Further purification of the residue was effected by converting the acid chloride groups into ethyl esters; the diester (e.g. 75) on hydrolysis gave the required diacid (72a) or (73a) (Scheme 29). The overall yields of (72a) or (73a) were very low and the whole process cumbersome, tedious and inefficient.

A modification of the method outlined in Scheme 28 gave m,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoic acid (74a) (Scheme 31) but the yield was again low.



(74a)

Scheme 31

When the second published route to (72a) or (73a) (Scheme 29)[18-22] was tried, the results obtained were again not very encouraging. The products obtained seemed again to be mixtures of compounds as judged by their melting behaviour (wide melting range or two distinct melting points for different parts of the

same sample).

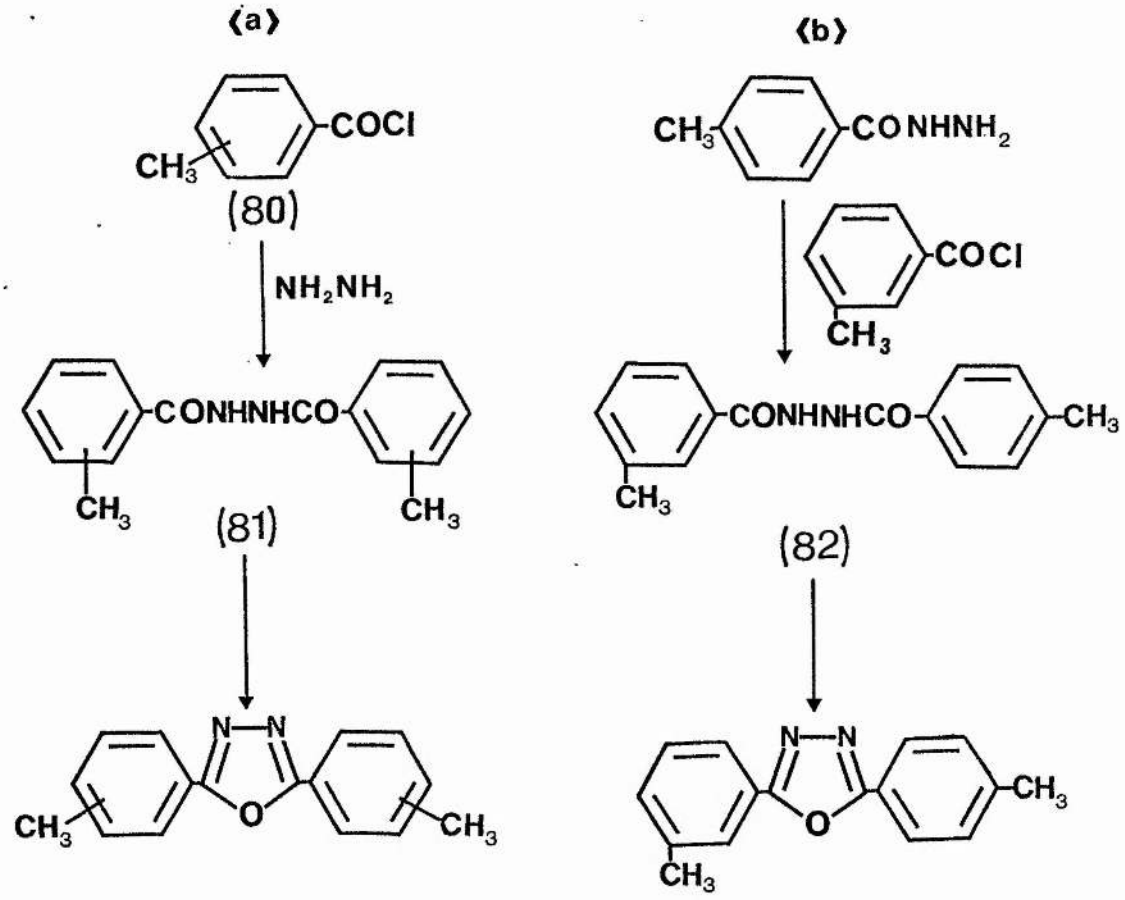
Purification of these compounds again required the same procedure as described earlier, of conversion to acid chlorides, esterification of the acid chloride and then hydrolysis of the ester to obtain pure product (72a) or (73a).

Again the yield was low and it required five to six steps depending on the starting material employed.

4.2 Synthesis

4.2.1 2,5-Ditolyl-1,3,4-oxadiazoles

The method which in our opinion is most suitable, economical and with fewest synthetic steps is outlined in scheme 32 (a and b).



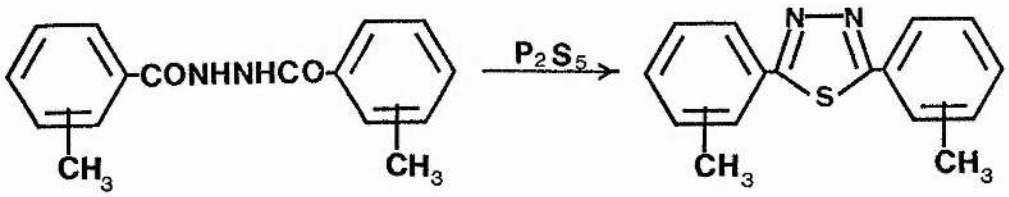
Scheme 32

2 mole equivalents of a toluoyl chloride (80) (meta- or para-) was converted into the corresponding ditoluoylhydrazine (cf. Chapter 1, p.3 and 4) and this on heating with thionyl chloride and a catalytic amount of pyridine gave the 2,5-ditolyl-1,3,4-oxadiazole.

Similarly by reacting m-toluoyl chloride (one mole equivalent) with p-toluoylhydrazine (one mole equivalent), 1-(p-toluoyl)-2-(m-toluoyl)hydrazine (82) was obtained which gave 2-(m-tolyl)-5-(p-tolyl)-1,3,4-oxadiazole on cyclisation.

4.2.2 2,5-Ditolyl-1,3,4-thiadiazoles

Similarly the thiadiazole analogues (83) could be prepared by heating the 1,2-ditoluoylhydrazine (81) or (82) with phosphorus pentasulphide in xylene (Scheme 33).

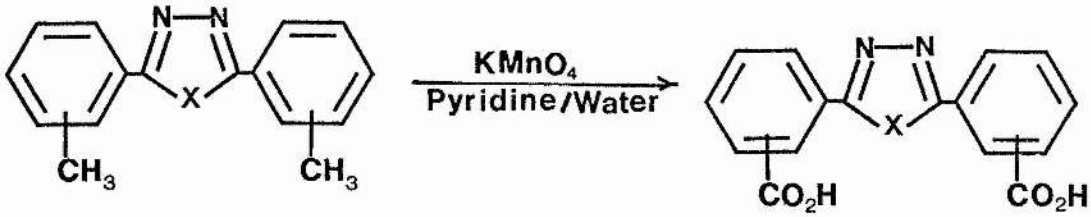


(81 or 82) (83b)

Scheme 33

4.2.3 Oxidation of 2,5-ditolyl-1,3,4-oxadiazoles and -thiadiazoles

The method used by Sokolenko and Suchilina[103] to oxidize side chains of benzenoid compounds was modified to meet our requirement. 2,5-Ditolyl-1,3,4-oxadiazoles and -thiadiazoles were oxidised to give (72-74 a and b) by heating them with potassium permanganate in an azeotropic mixture of pyridine and water (Scheme 34).



(83)

a: X = O

b: X = S

Scheme 34

4.2.4 General Discussion

The method outlined above, as compared to other literature methods, is shorter (three steps only). The overall yield is better. All the intermediate products can be purified by crystallisation and fully characterised. In view of the fact that these final products (72-74 a and b) are not sufficiently soluble in common solvents to permit easy recrystallisation, the high purity of the products in itself is a great advantage.

TABLE 15

(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acids and their thiadiazole analogues

Compound	Yield, %	M.p. (decomp.), °C‡	Formula	Analysis Found (crude product), %			Required, %		
				C	H	N	C	H	N
Oxadiazoles									
p,p	87	425 (lit.[16], 450°)	$C_{16}H_{10}N_2O_5$	61.4	3.4	8.9	61.9	3.25	9.0
m,m	80	362†(lit.[15], 368-371°)	"	†62.2	3.4	9.0	"	"	"
m,p	94	352	"	61.8	3.55	9.0	"	"	"
Thiadiazoles									
p,p	92	450	$C_{16}H_{10}N_2O_4S$	58.4	3.3	8.5	58.9	3.1	8.6
m,m	78	362	"	59.5	3.4	8.6	"	"	"
m,p	89	402	"	58.1	3.6	8.9	"	"	"

† Recrystallised from *N*-methylpyrrolid-2-one/water. All the other compounds were not recrystallised.

‡ Determined by differential thermal analysis: estimated error ±2°.

Yields and properties of (1,3,4-oxadiazole-2,5-diyl)dibenzoic acids and their thiadiazole analogues are tabulated in table 15.

As can be seen from the table all the acids are high-melting and normal melting point apparatus could not be employed for obtaining their melting points. New equipment developed in the Department of Chemistry, based on different thermal analysis[106], was used to record the melting points of these acids.

From our experience of literature methods of synthesis of these compounds, it should be said that the purity of the products obtained by these patent methods and consequently the polymers derived from these monomers must be open to question; also the polymers may not be structurally as homogeneous as has been claimed.

With the purity of the products obtained by this new method, it should now be possible to carry out property-structure relationship studies again, and the results reinterpreted or modified.

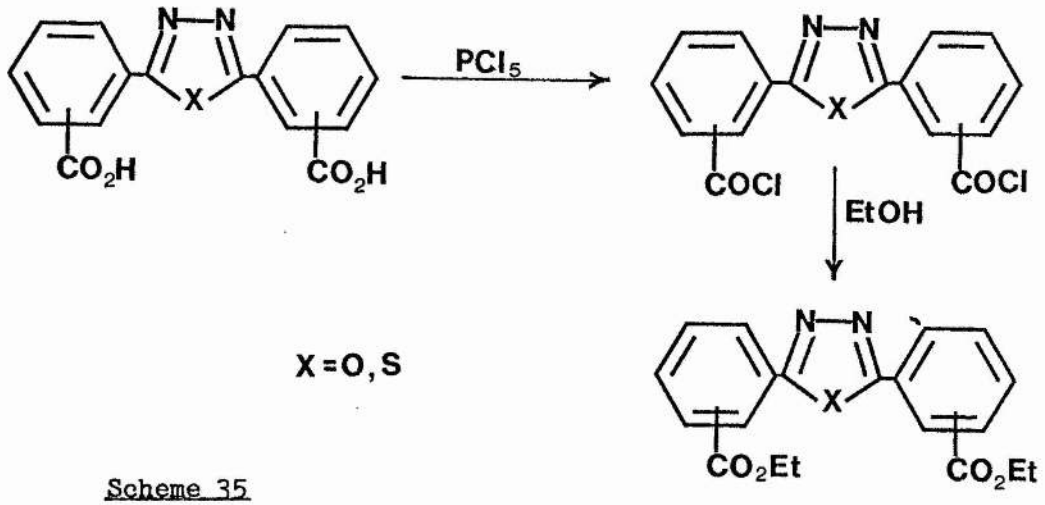
TABLE 16

Diethyl (1,3,4-oxadiazole-2,5-diyl)dibenzoates and their thiadiazole analogues

Corresponding acid	M.p., °C (from EtOH)	Formula	Found, %			Required, %		
			C	H	N	C	H	N
Oxadiazoles								
p,p	216-218 (lit.[14], 215)	$C_{20}H_{18}N_2O_5$	65.45	4.8	7.7	65.6	4.95	7.6
m,m	122-124 (lit.[15], 133-134)	"	65.25	4.8	7.9	"	"	"
m,p	147-149	"	66.0	5.0	7.65	"	"	"
Thiadiazoles								
p,p	266-268	$C_{20}H_{18}N_2O_4S$	62.8	4.7	7.4	62.8	4.7	7.3
m,m	125-127	"	63.2	4.8	7.45	"	"	"
m,p	120-122	"	62.5	4.6	7.4	"	"	"

4.3 Diethyl (1,3,4-oxadiazole-2,5-diyl)dibenzoates and their thiadiazole analogues

The diethyl esters of all the acids were prepared as shown in scheme 35 and the properties of these compounds are listed in table 16.



Scheme 35

4.4 ^{13}C NMR Spectra of Dipotassium Salts of Acids (72-74 a and b)

The dicarboxylic acids (72-74 a and b) can most simply be characterised by the ^{13}C NMR spectra of their dipotassium salts. The spectra of the six salts and provisional assignment of the individual resonances are shown in table 17.

The assignments are based on analogy with spectra of model compounds such as 2,5-diphenyl-1,3,4-oxadiazole and dipotassium

TABLE 17

^{13}C N.M.R. spectra of the di-potassium salts of (1,3,4-oxadiazole-2,5-diyl)dibenzoic acids and their thiadiazole analogues. (δ_C, ppm). ('Calculated' shifts using substituent parameters are shown in brackets)

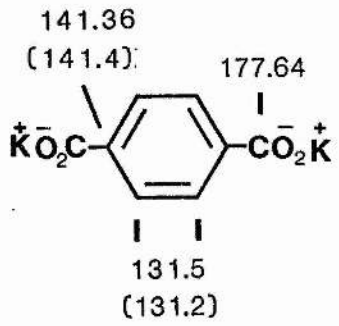
(a) Oxadiazoles Acid	CO_2^-	Heterocyclic carbon(s)	Benzenoid carbons			
			C-CO_2^-	C-heterocycle	C-H	
p,p	173.78	164.51	140.19 (140.2)	123.88 (124.2)	126.57(C-3 and C-5), (126.6)	129.55(C-2 and C-6) (129.6)
m,m	173.47	164.60	137.58 (137.3)	122.08 (121.7)	127.06(C-2), (126.8)	128.92(C-4), (129.0) 129.30(C-5), (129.3) 132.74(C-6) (132.5)
m,p	173.46	164.55	137.81(C-1') (137.3)	122.10(C-3') (121.7)	127.17(C-2'), (126.8)	128.90(C-4'), (129.0) 129.39(C-5'), (129.3) 132.86(C-6') (132.5)
	173.86	164.76	140.34(C-1) (140.2)	124.02(C-4) (124.2)	126.67(C-3 and C-5), (126.6)	129.63(C-2 and C-6) (129.6)
(b) Thiadiazoles						
p,p	173.82	169.36	139.48 (139.4)	130.29 (130.3)	127.43(C-3 and C-5), (127.4)	129.72(C-2 and C-6) (129.7)
m,m	173.59	169.56	137.54 (137.4)	128.27 (127.8)	127.99(C-2), (127.7)	129.30(C-5), (129.4) 129.68(C-4), (129.9) 132.03(C-6) (131.8)
m,p	173.65	169.30	137.59(C-1') (137.4)	128.30(C-3') (127.8)	128.18(C-2'), (127.7)	129.35(C-5'), (129.4) 129.66*(C-4'), (129.9) 132.06(C-6') (131.8)
	173.98	169.83	139.36(C-1) (139.5)	130.40(C-4) (130.3)	127.46(C-3 and C-5), (127.4)	129.66*(C-2 and C-6) (129.7)

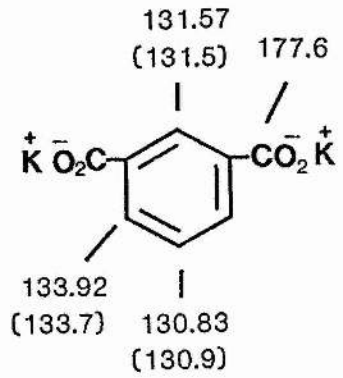
*Coincident resonances.

isophthalate and terephthalate, also on the well established principle[107] that the substituent effects on ^{13}C shielding/deshielding in benzene derivatives are approximately additive. The resonances of dipotassium isophthalate and terephthalate shown here correspond to approximate substituent parameters for the carboxylate ion (relative to δc = 128.5 for benzene) as follows:-

ipso-, +9.2; ortho-, +1.5; meta-, +1.2;

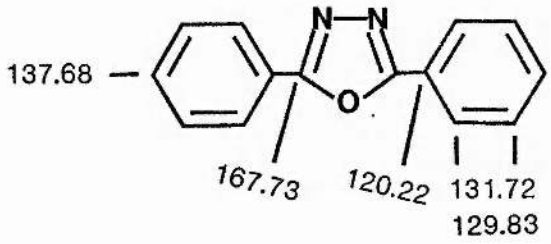
para-, +3.7.





[Calculated shifts using substituent parameters are shown in brackets]

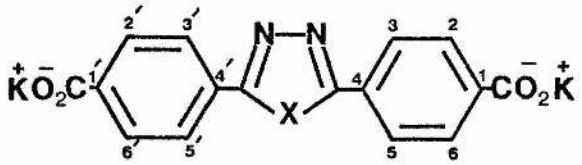
The ^{13}C resonances of unsubstituted 2,5-diphenyl-1,3,4-oxadiazole were obtained by Sagar[65] and are reproduced.

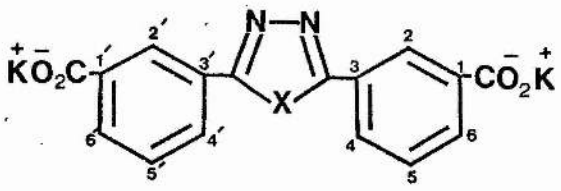


The following empirical substituent parameters for the heterocyclic substituents give 'calculated' chemical shifts for the benzenoid carbons of acids (72-74 a and b) which are in good agreement with the experimental data:-

a) 1,3,4-oxadiazole: ipso-, -8.0; ortho-, -3.2; meta-, -0.4; para-, +2.5.

b) 1,3,4-thiadiazole: ipso-, -1.9; ortho-, -2.3; meta-, -0.3; para-, +1.8.





a: X = O

b: X = S

chapter 5

Experimental

5.1 Material and Apparatus

Melting points were determined in open capillaries and are uncorrected. Infra red spectra were recorded for Nujol mulls using sodium chloride cells on a Perkin-Elmer 257 spectrophotometer and Perkin-Elmer 1310 IR spectrophotometer. Ultraviolet spectra were recorded on a Pye Unicam SP 800B instrument. Proton spectra were recorded at 60 MHz on a Varian EM 360 spectrometer and 80 MHz on Bruker-WP80 Fourier transform spectrometer for 10% solutions with tetramethylsilane as internal reference and sodium 3-(trimethylsilyl)-1-propanesulphonate as internal reference for spectra recorded in D_2O. ^{13}C NMR spectra were recorded at 20 MHz on a varian CFT 20 spectrometer or at 90.56 MHz by Dr. I. H. Sadler and his staff at the University of Edinburgh. Mass spectra were obtained on an AEI MS-902 spectrometer operating at 70 eV with source temperature of 200°C. Samples were introduced by means of a direct insertion probe.

High performance liquid chromatographs were taken with a Pye Unicam LC3 system using ultraviolet spectrophotometeric detector and a chart recorder. For normal phase separations a column of 'Partisil' 10 μm silica (25cm x 4.6 mm internal dia) and a solvent mixture of 20% 1,4-dioxan (Fisons SLR Grade dried over calcium hydride and redistilled) and 80% hexane (dried and

redistilled) was used (for nitration studies of thiadiazoles). The reverse phase chromatographic column used was 'Partisil ODS II' (loaded with 15% ODS; particle size 10 μm) (25cm x 5 mm i.d.) and a solvent system of 75% methanol and 25% water was used for the bromination products of oxadiazoles. The variable wavelength detector was set at 290 nm.

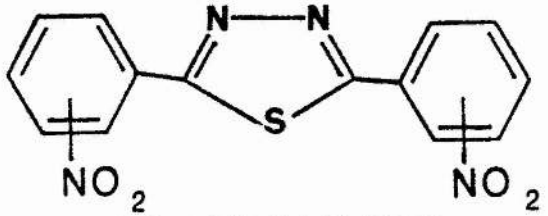
5.1.1 Determination of Product Ratios

The h.p.l.c. system, although a qualitative means of separation, was converted into a quantitative system by calibrating it using standards. Pure samples of all the products, independently synthesised, were used. Standard solutions of each compound, of the same molarity, were prepared and mixed in equal proportions to give a standard mixture.

In the case of the six bis-nitrophenyl-1,3,4-thiadiazoles, dioxan was used as the solvent. The curve obtained (figure 7) by h.p.l.c. analysis of the standard mixture was used to obtain a relative 'response factor' for each component, and these were then used to quantify the isomer ratios from the nitration mixtures. The separation of the peaks and their integration was carried out using a Du Pont 310 curve resolver (estimated error $< \pm 5\%$).

In the case of the bromination products described in chapter 3, methanol was used as the solvent. Standard solutions of the components were obtained, as above, and these were injected

LIQUID CHROMATOGRAM OF



COMPOUNDS

FIGURE 7

individually on to the column so that equimolar amounts of the components were used in each case. The peak area produced by these samples were compared on the curve resolver with a peak of known area (produced electrically) and the response factor calculated.

The above procedure was repeated three times on different days to check reproducibility. The area ratios obtained agree to within 5%.

5.1.2 Determination of pK_a's

UV spectra were taken as stated earlier on a Pye Unicam SP 800B spectrometer. The method used to determine the pK_a of the 2,5-diphenyloxazole (30) and 2,5-diphenyl-1,3,4-thiadiazole (45) is based on the H_o values of sulphuric acid in acetic acid as determined by Hall and Spengeman[87] (between 0.09 to 6.03). Using their data, solutions of AnalaR concentrated sulphuric acid (d 1.84) and AnalaR acetic acid (d 1.05) with varying H_o values were prepared. Solutions of known weights of the compounds (30 and 45) under investigation were prepared in acetic acid.

The same volume of solution was used for every measurement (1 ml) with a fixed volume of concentrated sulphuric acid/acetic acid mixture (2 ml). The H_o value of the mixture was recalculated. In the reference cell a mixture of similar value was used (acetic acid, 1 ml; sulphuric acid/acetic acid mixture

as used in the sample cell, 2 ml).

The H_o values were plotted against absorbance and the pK_a of the base was taken to be the H_o at half protonation (the H_o value halfway between the horizontal portion of the curve).

5.2 Abbreviations

s,	singlet
d,	doublet
t,	triplet
q,	quartet
m,	multiplet
br,	broad
aq,	aqueous
b.p.,	boiling point
d,	specific gravity
decomp.,	decomposition
DMF,	dimethylformamide
DMSO,	dimethyl sulphoxide
DTA,	differential thermal analysis
h.p.l.c.,	high performance liquid chromatography
m.p.,	melting point
petroleum	petroleum b.p.40/60

5.3 2,5-Diaryl-1,3,4-thiadiazoles

5.3.1 Preparation of Hydrazines

5.3.1.1 1,2-dibenzoylhydrazine

To a litre flask, cooled to 0°C, were added sodium hydroxide (250 ml; 2.4 M) and hydrazine sulphate (32.5 g; 0.25 mol) with stirring. Benzoyl chloride (77.3 g; 0.55 mol) was added dropwise to stirred solution over a period of 45 minutes and concurrenly aqueous sodium hydroxide (55 ml; 10M) was as well added dropwise . After stirring for 2 h, the solution was saturated with carbon dioxide. The white solid was filtered off and dried. 1,2-Dibenzoylhydrazine recrystallised from acetic acid, had m.p. 232-234°C (lit.[108] 234-238°); Yield 42 g (70%); $\nu_{max}(cm^{-1})$ (NH) 3210, (C=O) 1635.

5.3.1.2 1,2-Bis-(o-nitrobenzoyl)hydrazine

To a stirred solution of hydrazine hydrate (2.0 g; 0.04 mol) and anhydrous sodium carbonate (4.66 g; 0.044 mol) in DMF (100 ml) was added o-nitrobenzoyl chloride (16.0 g; 0.088 mol) with external cooling. After 4 h stirring, the suspension was added to water (100 ml), filtered and the residue washed with methanol and recrystallised from DMF/acetic acid. The product had m.p. 295-296°C (lit.[109] 289°); $\nu_{max}(cm^{-1})$ (NH) 3150, (C=O) 1620, (NO_2) 1520, 1350; Yield 7.4 g (56%).

5.3.1.3 1,2-Bis(m-nitrobenzoyl)hydrazine,

m.p. 240-242°C (from DMF/acetic acid; lit.[35] 242°); $\nu_{max}(cm^{-1})$ (NH) 3180, (C=O) 1610, (NO_2) 1520,1345, was similarly obtained from m-nitrobenzoyl chloride in 45% yield.

5.3.1.4 1,2-Bis(p-nitrobenzoyl)hydrazine,

m.p. 292-294°C (from DMF/acetic acid; Lit.[35] 296-297°); $\nu_{max}(cm^{-1})$ (NH) 3190, (C=O) 1615, (NO_2) 1520, 1345, was similarly obtained from p-nitrobenzoyl chloride in 53% yield.

5.3.1.5 m-Nitrobenzoylhydrazine

To a solution of hydrazine hydrate (20.0 g; 0.4 mol) in ethanol (40 ml) was added ethyl m-nitrobenzoate (26.0 g; 0.0135 mol). After heating under reflux for 1 h, the solution was cooled and the crude product filtered off, dried and recrystallised from water to give m-nitrobenzoylhydrazine, m.p. 150-152° (lit.[110] 152°); Yield 8.8 g (73%); $\nu_{max}(cm^{-1})$ (NH/NH_2) 3280, (C=O) 1630, (NO_2) 1525,1340.

5.3.1.6 p-Nitrobenzoylhydrazine,

m.p. 208-210° (from water; lit.[110] 210°); $\nu_{max}(cm^{-1})$ (NH/NH_2) 3310, (C=O) 1620, (NO_2) 1510, 1350, was similarly prepared from ethyl p-nitrobenzoate in 62% yield.

5.3.1.7 Benzoylhydrazine

To a solution of hydrazine hydrate (40.0 g; 0.8 mol) in ethanol (80 ml) was added ethyl benzoate (40.5 g; 0.27 mol) and the solution heated under reflux for 1 h. On cooling the solid was filtered off, washed with ice-cold ethanol and recrystallised from ethanol had m.p. 110-112°C (lit.[110] 113-117°); yield 37%

5.3.1.8 1-(o-Nitrobenzoyl)-2-(m-nitrobenzoyl)hydrazine,

To a stirred mixture of m-nitrobenzoylhydrazine (6.0 g; 0.033 mol), anhydrous sodium carbonate (3.51 g; 0.033 mol), and DMF (24 ml) was added dropwise a warm solution of o-nitrobenzoyl chloride (6.15 g; 0.033 mol) in xylene with external cooling. After 2 hours' stirring water (90 ml) was added together with hydrochloric acid (1M) to make it slightly acidic. The solid was filtered off, washed with boiling water and recrystallised from acetic acid/ethanol; m.p. 238-240°C (lit.[65] 236-238°); Yield 7.6 g (70%); $\nu_{max}(cm^{-1})$ (NH) 3150, (C=O) 1620, (NO_2) 1520, 1345.

5.3.1.9 1-(o-Nitrobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 282-284°C (from acetic acid; lit.[65] 280-282°); $\nu_{max}cm^{-1}$) (NH) 3190, (C=O) 1640, (NO_2) 1515, 1345, was similarly prepared in 70% yield.

5.3.1.10 1-(m-Nitrobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 246-248°C (from acetic acid; lit.[35] 251.5-252°); $\nu_{max}(cm^{-1})$ (NH) 3170, (C=O) 1605, (NO_2) 1520,1345, was similarly prepared in 74.5% yield.

5.3.1.11 1-Benzoyl-2-(o-nitrobenzoyl)hydrazine,

m.p. 210-212°C (from ethanol; lit.[111] 212-213°); $\nu_{max}(cm^{-1})$ (NH) 3230, (C=O) 1630, (NO_2) 1520,1345, was similarly prepared in 67% yield.

5.3.1.12 1-Benzoyl-2-(m-nitrophenyl)hydrazine,

m.p. 216-218°C (from ethanol/acetic acid; lit.[54] 216°); $\nu_{max}(cm^{-1})$ (NH) 3200, (C=O) 1640, (NO_2) 1525, 1350, was similarly prepared in 67% yield.

5.3.1.13 1-Benzoyl-2-(p-nitrobenzoyl)hydrazine,

m.p. 236-238°C (from acetic acid; lit.[112] 236°); $\nu_{max}(cm^{-1})$ (NH) 3200, (C=O) 1610, (NO_2) 1510, 1345, was similarly prepared in 58% yield.

5.3.2 Preparation of 2,5-diaryl-1,3,4-thiadiazoles

5.3.2.1 2,5-Diphenyl-1,3,4-thiadiazole (45)

1,2-Dibenzoylhydrazine (5.0 g) was heated under reflux with phosphorus pentasulphide (10.0 g) and redistilled xylene (60 ml) for 1 h. On cooling water (60 ml) and ether (50 ml) were added with stirring and the mixture left overnight; on filtration the solid so obtained recrystallised from ethanol, had m.p. 138-140°C (lit.[113] 141-142°); yield 2.77 g (54%); $\nu_{max}(cm^{-1})$ (thiadiazole)[114] 990.

5.3.2.2 2,5-Bis-(o-nitrophenyl)-1,3,4-thiadiazole (46)

1,2-Bis-(o-nitrobenzoyl)hydrazine (1.5 g), phosphorus pentasulphide (3.0 g) and redistilled xylene (25 ml) were heated under reflux for 1 h. On cooling water (50 ml) and ether (50 ml) were added with stirring and the mixture left overnight. The solid obtained on filtration was recrystallised from DMF and had m.p. 200-202°C; Yield 0.9 g (60%); $\nu_{max}(cm^{-1})$ (Thiadiazole) 990, (NO_2) 1530, 1350. (Found: C, 51.3; H, 2.3; N, 17.0. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.3 2,5-Bis(m-nitrophenyl)-1,3,4-thiadiazole (47),

m.p. 240-241°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 1000, (NO_2) 1525, 1345, was similarly prepared in 75% yield. (Found:C, 51.1;

H, 2.2, N, 17.1. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.4 2,5-Bis(p-nitrophenyl)-1,3,4-thiadiazole (48),

m.p. 326-328°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 990, (NO_2) 1525, 1340, was similarly prepared in 70% yield. (Found: C, 51.5; H, 2.4; N, 16.9. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.5 2-(o-Nitrophenyl)-5-(p-nitrophenyl)-1,3,4-thiadiazole(49),

m.p. 188-190°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 980, (NO_2) 1520, 1360, was similarly prepared in 58% yield. (Found: C, 51.2; H, 2.2, N, 16.8. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.6 2-(O-Nitrophenyl)-5-(p-nitrophenyl)-1,3,4-thiadiazole(50),

m.p. 192-194°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 990, (NO_2) 1515, 1350, was similarly prepared in 53% yield. (Found: C, 51.1; H, 2.5; N, 16.8. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.7 2-(m-Nitrophenyl)-5-(p-nitrophenyl)-1,3,4-thiadiazole(51),

m.p. 244-246°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 980, (NO_2) 1520, 1355, was similarly prepared in 79% yield. (Found: C,

51.2; H, 2.2; N, 17.0. $C_{14}H_8N_4O_4S$ requires C, 51.2; H, 2.5; N, 17.1%).

5.3.2.8 2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole(52),

m.p. 138-140°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 980, (NO_2) 1510, 1355, was similarly prepared in 48% yield. (Found: C, 59.4; H, 3.0; N, 14.6. $C_{14}H_9N_3O_2S$ requires C, 59.35; H, 3.2; N, 14.8%).

5.3.2.9 2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole(53),

m.p. 192-194°C (from DMF); $\nu_{max}(cm^{-1})$ (Thiadiazole) 990, (NO_2) 1520, 1355, was similarly prepared in 58% yield. (Found: C, 59.4; H, 3.1; N, 14.6. $C_{14}H_9N_3O_2S$ requires C,59.35; H, 3.2; N, 14.8%).

5.3.2.10 2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole(54),

m.p. 257-259°C (from DMF/acetic acid); $\nu_{max}(cm^{-1})$ (Thiadiazole) 980, (NO_2) 1525, 1350, was similarly prepared in 62% yield. (Found: C, 59.4; H, 3.1; N, 14.6. $C_{14}H_9N_3O_2S$ requires C, 59.35; H, 3.2; N, 14.8%).

5.4 2-Bromo-/dibromophenyl-5-(p-nitrophenyl)-1,3,4-thiadiazoles

5.4.1 Dibromo- and tribromobenzoic acids

2,3-Dibromobenzoic Acid

5.4.1.1 2-Bromo-3-nitrotoluene[115]

2-Methyl-6-nitroaniline (5.0 g; 0.033 mol), finely divided, was suspended in a mixture of hydrobromic acid (40%, 6 ml), water (9 ml),and cooled to 0°C. It was diazotised with sodium nitrite (2.7 g; 0.039 mol) in water (4 ml) at 0°C. The filtered diazonium solution was run rapidly, with constant stirring, into a solution of copper(I) bromide [prepared by saturating with sulphur dioxide a mixture of copper(II) sulphate (6.0 g) in water (20 ml) and potassium bromide (3.0 g) in water (7 ml)] in hydrobromic acid (11 ml) without external cooling. After 30 minutes' stirring, the mixture was heated in a steam bath for a further 30 minutes and the product steam distilled. The distillate was made basic with sodium hydroxide, cooled, and the resulting solid dissolved in ether. The ether solution was washed with sodium hydroxide (1 M), dried (magnesium sulphate), evaporated at low temperature and the residual liquid crystallised on addition of petroleum. Yield 4.9 g (69%); m.p. 40-42°C (lit.[115] 40-42°).

5.4.1.2 2-Bromo-3-methylaniline hydrobromide[116]

In a round-bottomed flask equipped with a reflux condenser were placed 2-bromo-3-nitrotoluene (5.4 g; 0.025 mol) and granulated tin (4.5 g; 0.038 mol). Concentrated hydrobromic acid (15 ml) was poured through the condenser with shaking at 40-50°C until all the acid had been added. Stirring was continued at 40-50°C for 1 h, an additional portion of hydrobromic acid (15 ml) was added, and heating on a water bath continued for a short time (20-30 minutes). The mixture was cooled to room temperature, sodium hydroxide (20.0 g) in water (35 ml) added and the product steam distilled. The organic distillate was dissolved in ether, and concentrated hydrobromic acid added, and the hydrobromide filtered off. Yield 5.8 g (87%).

5.4.1.3 2,3-Dibromotoluene[115]

This was prepared as in 5.4.1.1 from 2-bromo-3-methylaniline hydrobromide (4.3 g; 0.016 mol), hydrobromic acid (40% 5 ml), water (9 ml), sodium nitrite (1.4 g; 0.02 mol in 2 ml of water). Yield 2.1 g (53%). m.p. around room temperature (lit.[117] 30-31°).

5.4.1.4 2,3-Dibromobenzoic Acid[103,118]

Potassium permanganate (3.0 g) was added to a well-stirred mixture of 2,3-dibromotoluene (2.0 g) in pyridine (18 ml) and

water (12 ml) at 70°C. The mixture was heated under reflux for 2 h, evaporated to dryness in vacuum, the residue extracted with water and the extract acidified (2 M HCl). The precipitated acid recrystallised from water had a m.p. 139-140°C (lit.[119] 149-150°); Yield 0.5 g (23%).

2,4-Dibromobenzoic Acid

5.4.1.5 2,4-Dibromobenzonitrile[120]

2,4-Dibromoaniline (8.3 g; 0.033 mol), concentrated hydrochloric acid (8.5 ml) and water (14 ml) were heated with stirring to form a solution, then cooled to 0°C, and ice (20.0 g) added. A solution of sodium nitrite (2.4 g; 0.04 mol in water 5 ml cooled to 0°C) was added dropwise with stirring. The mixture was neutralised with sodium carbonate (Ca. 2.2 g). The solution was added to a warm solution of (60-70°C) copper(I) cyanide [prepared by dissolving copper(I) cyanide (3.6 g) and potassium cyanide (5.2 g) in water (12.5 ml)] on a water bath with vigorous stirring. The resulting mixture was heated on a water bath for 30 minutes and the product was steam distilled and recrystallised from petroleum (b.p. 60-80°C). Yield 2.8 g (33%). m.p.95-96°C (lit.[121] 93-94°).

5.4.1.6 2,4-Dibromobenzoic Acid

2,4-Dibromobenzonitrile (2.8 g; 0.011 mol), sodium hydroxide (6.0 g; 0.15 mol), water (60 ml) and ethanol (10 ml) were heated

under reflux for 2 h, then cooled and filtered and the filtrate acidified with hydrochloric acid (3 M). The product was recrystallised from benzene. Yield 2.0 g (70%), m.p. 170-172°C (lit.[119] 168-169°). $\nu_{max}(cm^{-1})$ (C=O) 1660.

2,5-Dibromobenzoic Acid

5.4.1.7 2,5-Dibromobenzoic Acid[122]

Bromine (8.0 g; 0.05 mol) was added to a solution of o-bromobenzoic acid (10.0 g; 0.05 mol) in a mixture of acetic acid (150 ml), concentrated nitric acid (32 ml) and water (26 ml). To this solution was added dropwise with vigorous stirring a solution of silver nitrate (8.5 g; 0.05 mol) in water (50 ml). After 15 minutes of stirring, the reaction mixture was filtered and reduced in vacuum to one half, then diluted with water and precipitate so formed collected by filtration. Recrystallised from water, it had m.p. 154-155°C (lit.[122] 158-160°); Yield 6.1 g (44%).

2,6-Dibromobenzoic Acid

5.4.1.8 3,5-Dibromosulphanilamide

To a solution of sulphanilamide (50.0 g; 0.29 mol) in water (850 ml) was added hydrobromic acid (48% 75 ml; 0.68 mol) and the solution was heated to 70°C. Hydrogen peroxide (30% 59 ml; 0.58 mol) was added dropwise with stirring and a precipitate formed

within five minutes. Stirring was continued for 30 minutes and the product filtered off and recrystallised from 95% ethanol. Yield 47.0 g (49%); m.p. 238-240°C (lit.[123] 239-240°).

5.4.1.9 2,6-Dibromoaniline

3,5-Dibromosulphanilamide (40.0 g; 0.12 mol) and concentrated sulphuric acid (80% 360 ml) were heated on an oil bath to 170°C in a flask fitted with a reflux condenser. Steam was then passed rapidly for 2 h at the end of which the oil bath was removed. 2,6-Dibromoaniline was then isolated by steam distillation and recrystallised from ethanol (75%). Yield 21.1 g (69%); m.p. 76-78°C (lit.[123] 87-88°).

5.4.1.10 2,6-Dibromobenzonitrile

This was prepared as 5.4.1.5 from 2,6-dibromoaniline in 21% yield, and had m.p. 149-150°C (lit.[124] 155°).

5.4.1.11 2,6-Dibromobenzamide[124]

2,6-Dibromobenzonitrile (2.6 g), concentrated sulphuric acid (30 ml), acetic acid (30 ml) and water (30 ml) were heated under reflux for 8 h, cooled and ice (20 g) added. The precipitate formed was collected. A further quantity was recovered by extracting the filtrate with chloroform and the normal work up. Recrystallised from water, it had m.p. 205-206°C (lit.[124] 208.5°); yield 1.6 g (58%).

5.4.1.12 2,6-Dibromobenzoic Acid[124]

2,6-Dibromobenzamide (0.4 g; 0.0014 mol) and sulphuric acid (90%; 7ml) was heated to 60-70°C. Sodium nitrite (0.42 g; 0.006 mol) was added with stirring over a period of 1 h. The mixture was poured into ice and the product recrystallised from water. Yield 0.25 g (61%); m.p. 144-145°C (lit.[124] 146-147°); $\nu_{max}(cm^{-1})$ (C=O) 1720.

3,4-Dibromobenzoic Acid

5.4.1.13 3,4-Dibromobenzoic Acid

Bromine (12.0 g; 0.15 mol) was added to a solution of p-bromobenzoic acid (15.5 g; 0.075 mol), acetic acid (450 ml), concentrated nitric acid (48 ml) and water (39 ml) with stirring. To this solution was added dropwise a solution of silver nitrate (12.75 g; 0.075 mol) in water (75 ml). After 30 minutes' stirring, the reaction mixture was filtered off, the filtrate concentrated and diluted with water to give a precipitate. The organic solid left in the first filtration was extracted with hot ethanol and this extract on dilution gave a further precipitate. Recrystallisation of the combined precipitates from ethanol gave 12.0 g of the acid. Yield 57%; m. p. 218-220°C (lit.[119] 229-230°); $\nu_{max}(cm^{-1})$ (C=O) 1680.

3,5-Dibromobenzoic Acid

5.4.1.14 3,5-Dibromoanthranilic Acid

Anthranilic acid (20.0 g; 0.145 mol), water (425 ml) and hydrobromic acid (48% 37.5 ml; 0.34 mol) were heated to 70°C. Hydrogen peroxide (30% 30 ml; 0.29 mol) was added dropwise with stirring. A precipitate formed (5-10 minutes). Stirring was continued for another 2 h. and the precipitate was filtered off and recrystallised from acetic acid. Yield 24.0 g; (65%); m.p. 235-236°C (lit.[119] 239-240°).

5.4.1.15 3,5-Dibromobenzoic Acid

3,5-Dibromoanthranilic acid (7.85 g; 0.03 mol) was dissolved with gentle warming in ethanol (60 ml) and benzene (15 ml). The solution was cooled to room temperature and sodium nitrite (3.5 g; 0.05 mol) added. The mixture was heated on a water bath for 3-4 h, cooled, and the solid so obtained crystallised from benzene. Yield 3.4 g (45%); m.p. 212-213°C (lit.[119] 213-214°); $\nu_{max}(cm^{-1})$ (C=O) 1700.

3,4,5-Tribromobenzoic Acid

5.4.1.16 2,6-Dibromo-p-toluidine

This was prepared as in 5.4.1.13 from p-toluidine (15.54 g;

0.145 mol) in 80% yield, had m.p. 70-72°C (from ethanol; lit.[117] 74-75°).

5.4.1.17 3,4,5-Tribromotoluene

This was prepared as in section 5.4.1.1 from 2,6- dibromo-p-toluidine (8.7 g; 0.033 mol) in 55% yield; had m.p. 76-78°C (from ethanol; lit.[117] 88-89°).

5.4.1.18 3,4,5-Tribromobenzoic acid

This was prepared as in 5.4.1.4 from 3,4,5-tribromotoluene in 27% yield; it had m.p. 237-238°C (from benzene; lit.[117] 235°); $\nu_{max}(cm^{-1})$ (C=O) 1700.

5.4.2 Dibromo- and Tribromobenzoyl Chlorides

5.4.2.1 2,3-Dibromobenzoyl chloride

2,3-Dibromobenzoic acid (0.5 g) and phosphorus pentachloride (0.6 g) were melted over a flame (time required 5-10 minutes). The melt was allowed to cool, phosphorus oxychloride was evaporated and the solid formed on cooling extracted with benzene. The benzene was evaporated and on addition of petroleum and cooling the residue formed crystals. Recrystallised from petroleum, it had m. p. 57-59°C (lit.[119] 60-62°); Yield 0.5 g (94%).

5.4.2.2 2,4-Dibromobenzoyl chloride,

m.p. 50-52°C (from petroleum; lit.[119] 43-45°); was similarly obtained in 96% yield.

5.4.2.3 2,5-Dibromobenzoyl chloride,

m.p. 44-45°C (from petroleum; lit.[119] 39-41°); was similarly obtained in 92% yield.

5.4.2.4 2,6-Dibromobenzoyl chloride,

m.p. 35-36°C (from petroleum; lit.[119] 39-40°); was similarly obtained in 94% yield.

5.4.2.5 3,4-Dibromobenzoyl chloride,

m.p. 62-64°C (from petroleum; lit.[119] 64-66°); was similarly prepared in 63% yield.

5.4.2.6 3,5-Dibromobenzoyl chloride,

m.p. 32-35°C (from petroleum; lit.[119] 41-42°); was similarly prepared in 80% yield.

5.4.2.7 3,4,5-Tribromobenzoyl chloride,

m.p. 70-72°C (from petroleum; lit.[125] 83°); was similarly prepared in 87% yield.

5.4.3 1-(Mono-/di-/tribromobenzoyl)-2-(p-nitrobenzoyl)hydrazines

5.4.3.1 1-(o-Bromobenzoyl)-2-(p-nitrobenzoyl)hydrazine

p-Nitrobenzoylhydrazine (6.0 g; 0.033 mol), anhydrous sodium carbonate (3.6 g; 0.034 mol), and DMF (50 ml) were stirred with external cooling. A warm solution of o-bromobenzoyl chloride in a small volume of xylene was added dropwise, stirring continued for 4 h and the mixture poured into water (200 ml), made slightly acidic with dilute hydrochloric acid, and the product filtered off and recrystallised from acetic acid. It had m.p. 250-252°C; Yield 9.2 g (77%); $\nu_{max}(cm^{-1})$ (NH) 3160, (C=O) 1585, 1610, (NO_2) 1530,1340. (Found: C, 46.4; H, 2.8; N, 11.6. $C_{14}H_{12}BrN_3O_4$ requires C, 46.2; H, 2.8; N, 11.5%).

5.4.3.2 1-(m-Bromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 213-215°C (from acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3190, (C=O) 1585,1610, (NO_2) 1520,1340, was similarly prepared in 79% yield. (Found: C, 46.45; H, 2.8; N, 11.6. $C_{14}H_{12}BrN_3O_4$ requires C, 46.2; H, 2.8; N, 11.5%).

5.4.3.3 1-(p-Bromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 300-302°C (from DMF/acetic acid; lit.[65] 292-294°); $\nu_{max}(cm^{-1})$ (NH) 3180, (C=O) 1585,1610, (NO_2) 1520,1340, was similarly prepared in 55% yield.

5.4.3.4 1-(2,3-Dibromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 258-260°C (from acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3200, (C=O) 1630, 1690, (NO_2) 1518, 1340, was similarly prepared in 67% yield. (Found: C, 37.7; H, 2.1; N, 9.4. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95; H, 2.05; N, 9.5%).

5.4.3.5 1-(2,4-Dibromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 254-256°C (from acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3230, (C=O) 1685, 1640, (NO_2) 1522, 1342, was similarly prepared in 70% yield. (Found: C, 37.6; H, 2.1; N, 9.35. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95; H, 2.05; N, 9.5%).

5.4.3.5 1-(2,5-Dibromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 264-265°C (from dilute acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3230, (C=O) 1650, 1690, (NO_2) 1530, 1330, was similarly prepared in 70% yield. (Found: C, 37.8; H, 2.0; N, 9.3. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95; H, 2.05; N, 9.5%).

5.4.3.7 1-(2,6-Dibromobenzoyl)-2-(p-nitrophenyl)hydrazine,

m.p. 314-316°C (from dilute acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3160, (C=O) 1610, 1590, (NO_2) 1510,1345, was similarly prepared in 65% yield. (Found: C,37.5; H, 2.0; N, 9.4. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95; H, 2.05, N, 9.5%).

5.4.3.8 1-(3,4-Dibromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 266-268°C (from acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3180, (C=O) 1610, 1590, (NO_2) 1510, 1345, was similarly obtained in 63% yield. (Found: C, 38.5; H, 2.0; N, 9.4. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95; H, 2.05, N, 9.5%).

5.4.3.9 3,5-(Dibromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 256-258°C (from acetic acid/DMF); $\nu_{max}(cm^{-1})$ (NH) 3180, (C=O) 1640, (NO_2) 1515, 1340, was similarly prepared in 48% yield. (Found: C, 37.6; H, 2.1; N, 9.2. $C_{14}H_{11}Br_2N_3O_4$ requires C, 37.95, H, 2.05, N, 9.5%).

5.4.3.10 1-3,4,5-Tribromobenzoyl)-2-(p-nitrobenzoyl)hydrazine,

m.p. 257-258°C (from acetic acid); $\nu_{max}(cm^{-1})$ (NH) 3200, (C=O) 1690, 1650, (NO_2) 1525, 1345, was similarly obtained in 73% yield. (Found C, 32.0; H, 1.55; N, 84.0. $C_{14}H_{10}Br_3N_3O_4$ requires C, 32.2; H, 1.5; N, 8.05%).

5.4.4 2-(Phenyl/di-/tribromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazoles

5.4.4.1 2-Phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole(44)

1-Benzoyl-2-(p-nitrobenzoyl)hydrazine (7.5 g), thionyl chloride (60 ml), and pyridine (0.5 ml) were heated under reflux for 1.5 h. Thionyl chloride was evaporated in vacuo and the oxadiazole, recrystallised from acetone, had m. p. 206-208°C (lit.[126] 206.5-208°); Yield 5.15 g (73%); $\nu_{max}(cm^{-1})$ (oxadiazole) 960, (NO_2) 1505, 1335.

5.4.4.2 2-(o-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(61),

m.p. 184-186°C (from DMF/acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 965, (NO_2) 1510, 1340, was similarly prepared in 87% yield. (Found: C, 48.45; H, 2.3; N, 12.1. $C_{14}H_{10}BrN_3O_3$ requires C, 48.6; H, 2.3; N, 12.1%).

5.4.4.3 2-(m-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(62),

m. p. 202-203°C (from DMF/acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 965, (NO_2) 1520,1340, was similarly obtained in 74% yield. (Found: C, 48.3; H, 2.3; N, 12.0. $C_{14}H_{10}BrN_3O_3$ requires C, 48.6; H, 2.3; N, 12.1%).

5.4.4.4 2-(p-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(63),

m.p. 248-250° (from DMF/acetic acid; lit.[65] 240-242°); ν_{max}(cm^{-1}) (oxadiazole) 965, (NO_2) 1520, 1340, was similarly prepared in 59% yield.

5.4.4.5 2-(2,3-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(64),

m.p. 226-228°C (from acetic acid); ν_{max}(cm^{-1}) (oxadiazole) 970, (NO_2) 1530, 1340, was similarly prepared in 75% yield. (Found: C, 39.3; H, 1.7; N, 9.8. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%).

5.4.4.6 2-(2,4-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(67),

m.p. 194-196°C (from acetic acid); ν_{max}(cm^{-1}) (oxadiazole) 970, (NO_2) 1515, 1345, was similarly prepared in 65% yield. (Found: C, 39.3; H, 1.6; N, 9.8. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%).

5.4.4.7 2-(2,5-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(65),

m.p. 239-240°C (from acetic acid); ν_{max}(cm^{-1}) (oxadiazole) 970, (NO_2) 1520, 1340, was similarly prepared in 50% yield. (Found: C, 39.35; H, 1.7; N, 9.9. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%).

5.4.4.8 2-(2,6-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(69),

m.p. 270-272°C (from dilute acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 970, (NO_2) 1520, 1340, was similarly prepared in 50% yield. (Found: C, 39.35; H, 1.7; N, 9.85. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%).

5.4.4.9 2-(3,4-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(66),

m.p. 246-248°C (from acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 965, (NO_2) 1510, 1340, was similarly prepared in 42% yield. (Found: C, 39.2; H, 1.7; N, 9.8. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N, 9.9%).

5.4.4.10 2-(3,5-Dibromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(68),

m.p. 226-228°C (from DMF/acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 970, (NO_2) 1515, 1340, was similarly prepared in 49% yield. (Found: C, 39.5; H, 1.7; N, 9.8. $C_{14}H_9Br_2N_3O_3$ requires C, 39.6; H, 1.7; N,9.9%).

5.4.4.11 2-(3,4,5-Tribromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole (70)

m.p. 272-274°C (from acetic acid); $\nu_{max}(cm^{-1})$ (oxadiazole) 960, (NO_2) 1517, 1340, was similarly prepared in 23% yield. (Found: C, 33.0; H, 1.5; N, 8.1. $C_{14}H_8Br_3N_3O_3$ requires C, 33.4; H, 1.2; N, 8.3%).

5.5 (1,3,4-Oxadiazole-2,5-diyl)dibenzoic acids, thiadiazole analogues and their ethyl esters

5.5.1 Literature Methods

5.5.1.1 Oleum method

5.5.1.1.1 p,p'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid(72a)

Terephthalic acid (20.9 g) was introduced in small portions into a solution of hydrazine sulphate (7.8 g) in oleum (60 ml) containing sulphur trioxide (25%) with stirring and external cooling to keep the the temperature below 20°C. After the addition of terephthalic acid was completed, the temperature was slowly raised to 55°C (30 minutes). Stirring of the mixture was continued for 6 h at 55-65°C. The mixture was then poured into an ice-water mixture. The product was separated by centrifuging, decantation, and again mixing with water and centrifuging again. The process of mixing with water and centrifuging was carried out three times. The solid so obtained was sucked dry on a sintered funnel, and finally dried in an oven at 100°C. The solid was redissolved as far as possible, in sodium carbonate (1M), filtered, and the acidic material reprecipitated with hydrochloric acid (2M); the yield was 13.2 g.

Ten grams of this material was melted with phosphorus pentachloride (20.0 g) and the mixture was heated under reflux

for 1 h, then cooled. Petroleum (50 ml) was added, the mixture then refluxed for further 1 h, and filtered hot; cooling of the filtrate gave terephthaloyl chloride (4.0 g) m.p. 84-86°C. [(lit.[127] 83-84°), identical in all respects with an authentic sample].

The petroleum-insoluble product was heated under reflux for 2 h with dry ethanol (200 ml), and the resulting mixture also filtered hot. The filtrate on cooling gave the diethyl esters of (72a); m.p. 216-218°C (lit.[127] 215°). Extraction of the solid residue with hot DMF gave a further crop (0.35 g) of the ester. There remained a high melting residue (1.95 g).

Diethyl p,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoate (1.03 g), potassium hydroxide (0.37 g) and 60% ethanol (50 ml) were heated under reflux for 10 h, cooled, and the solid obtained on addition of hydrochloric acid (6M) was filtered off, washed with water and dried; Yield 0.7 g.

5.5.1.1.2 m,m'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid(73a),

was prepared similarly from isophthalic acid (26.0 g). The total yield of the acidic material was 10.2 g.

Ten grams was converted to the diethyl ester of (73a) as in 5.5.1.1.1; Yield 0.3 g; m.p. 122-124°C (from dilute ethanol; lit.[17] 133-134°). Isophthaloyl dichloride (7.5 g) and a high melting residue (1.06 g) were also obtained.

5.5.1.2 Second Literature Method

5.5.1.2.1 Terephthaloyl chloride

Terephthalic acid (15.0 g) and phosphorus pentachloride (37.5 g) were heated in an oil bath till melted and then heated under reflux for 1/2 h. Petroleum (150 ml) was added and the mixture heated under reflux for a further 1/2 h, and filtered hot. The solid obtained on cooling was washed with ice-cold petroleum, dried and had m.p. 77-79°C (lit.[22] 79-81°); Yield 9.7 g (53%).

5.5.1.2.2 p-(Methoxycarbonyl)benzoyl chloride

To a mixture of benzene (20 ml) and terephthaloyl chloride (10.32 g) was added dry methanol (2 ml) with stirring and the solution stirred for 2 h at 80°C. It was heated under reflux for $1^1/2$ h, cooled and filtered. The filtrate was diluted with petroleum (20 ml) and concentrated to ca. 10 ml, cooled in an ice bath, filtered, and the solid product dried. Yield 6.8 g (63%); m.p. 38-40°C (lit.[128] 38-40°).

5.5.1.2.3 1,2-Di-(p-methoxycarbonylbenzoyl)hydrazine

To a solution of hydrazine hydrate (0.5 g; 0.02 mol), and sodium bicarbonate (1.5 g; 0.02 mol) in water (15 ml) was added dropwise over a period of 15 minutes with stirring a solution of

p-(methoxycarbonyl)benzoyl chloride (4.0 g; 0.02 mol) in THF (15 ml) while keeping the temperature of the mixture between 30-40°C. Stirring of the mixture was continued for another 30 minutes at the end of which water (50 ml) was added, the mixture cooled and the product filtered off. The solid so obtained was washed with water and then with methanol and dried. Yield 3.1 g. Part of the sample melted at 206-210°C and the remainder melted at 290-295°C. (lit.[127] 268-270°).

5.5.1.2.3 Dimethyl p,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoate

1,2-Di-(p-methoxycarbonylbenzoyl)hydrazine (5.0 g), phosphorus oxychloride (25 ml) and toluene (50 ml) were heated under reflux for 6 h, cooled and the solid filtered off, washed with water and dried. Yield 2.75 g. Part of the sample melted at 250-260°C and the remainder at 300-305°C. (lit.[17] 268-270°).

5.5.2 Toluoylhydrazines

5.5.2.1 1,2-Di-p-toluoylhydrazine

To a stirred solution of hydrazine hydrate (2.0 g; 0.04 mol), and anhydrous sodium carbonate (4.66 g; 0.044 mol) in ethanol (100 ml) was added dropwise p-toluoyl chloride (13.6 g; 0.088 mol) with external cooling. Stirring of the mixture was continued for 6 h with external cooling. The suspension was added to water (350 ml), made slightly acidic with hydrochloric

acid (2M), filtered, and the precipitate washed with water and recrystallised from ethanol. Yield 8.4 g (78%); m.p. 252-254°C (lit.[129] 253-254°); ν_{max}(cm^{-1}) (NH) 3190, (C=O) 1630.

5.5.2.2 1,2-Di-m-toluoylhydrazine,

was similarly prepared; it had m. p. 223-224°C (from ethanol; lit.[130] 214-216°); Yield 77%; ν_{max}(cm^{-1}) (NH) 3210, (C=O) 1640.

5.5.2.3 1-(p-toluoyl)-2-(m-toluoyl)hydrazine

p-Toluoylhydrazine (9.0 g; 0.06 mol), anhydrous sodium carbonate (6.36 g; 0.06 mol), and dry ethanol (150 ml) were stirred with external cooling. To this mixture was added dropwise m-toluoyl chloride (9.3 g; 0.06 mol), and stirring continued for 4 h. The mixture was poured into water (300 ml), made slightly acidic by adding dilute hydrochloric acid and filtered. The solid so obtained was washed with water and recrystallised from ethanol. Yield 13.0 g (77%); m.p. 232-234°C; ν_{max}(cm^{-1}) (NH) 3200, (C=O) 1635. (Found: C, 71.6; H, 6.0; N, 10.4. $C_{16}H_{16}N_2O_2$ requires C, 71.9; H, 6.1; N, 10.5%).

5.5.3 2,5-Ditolyl-1,3,4-oxadiazoles

5.5.3.1 2,5-Di-(m-tolyl)-1,3,4-oxadiazole

1,2-Di-m-toluoylhydrazine (15.0 g), thionyl chloride (200

ml), and pyridine (20 drops) were heated under reflux for 2 h. Thionyl chloride was evaporated under vacuum, the last traces being removed by co-distillation with benzene (20 ml). The solid so obtained, recrystallised from ethanol, had m.p. 81-82°C (lit.[130] 72°); Yield 11.2 g (80%), $\nu_{max}(cm^{-1})$ (oxadiazole) 960.

5.5.3.2 2,5-(p-tolyl)-1,3,4-oxadiazole,

m.p. 176-177°C (from petroleum; lit.[130] 175°); Yield 10.9 g (78%); $V_{max}(cm^{-1})$ (oxadiazole) 970, was similarly prepared.

5.5.3.3 2-(m-Tolyl)-5-(p-tolyl)-1,3,4-oxadiazole,

m.p. 84-86°C (from petroleum); Yield 11.2 (80%); $V_{max}(cm^{-1})$ (oxadiazole) 970, was similarly prepared. (Found: C, 77.0; H, 5.6; N, 11.1. $C_{16}H_{14}N_2O$ requires C, 76.8; H, 5.6; N, 11.2%).

5.5.4 2,5-Ditolyl-1,3,4-thiadiazole

5.5.4.1 2,5-Di-(m-tolyl)-1,3,4-thiadiazole

1,2-Di-m-toluoylhydrazine (30.0 g), phosphorus pentasulphide (30.0 g), and xylene (250 ml) were heated under reflux for 2 h, allowed to cool, water (150 ml) was added and the mixture left overnight. The solid obtained on filtration was extracted with ether (3x100 ml). The ether extract was washed with sodium hydroxide (3x5 ml; 1M) and then with water, dried over magnesium

sulphate and the ether evaporated at low temperature. The syrupy liquid so obtained on addition of petroleum (75 ml) gave crystals of the desired product.

The ether-insoluble solid left from the original reaction mixture was again extracted with hot DMF and on dilution with water a second crop of thiadiazole obtained and recrystallised from petroleum (60-80°C). Yield 15.7 g (53%); m. p. 90-92°C; $\nu_{max}(cm^{-1})$ (thiadiazole) 980. (Found: C, 72.1; H, 5.3; N, 10.4. $C_{16}H_{14}N_2S$ requires C, 72.2; N, 5.3; N, 10.5%).

5.5.4.2 2,5-Di-(p-tolyl)-1,3,4-thiadiazole,

m.p. 165-166°C (from ethanol; lit.[130] 156-158°); $\nu_{max}(cm^{-1})$ (thiadiazole) 990, was similarly prepared in 54% yield.

5.5.4.3 2-(m-Tolyl)-5-(p-tolyl)-1,3,4-thiadiazole,

m. p. 125-126°C (from petroleum b.p. 60-80°C); $\nu_{max}(cm^{-1})$ (thiadiazole) 970, was similarly prepared in 60% yield. (Found:C, 72.5; H, 5.2; N, 10.5. $C_{16}H_{14}N_2S$ requires C, 72.2; H, 5.3; N, 10.5%).

5.5.5 1,3,4-Oxadiazole-2,5-diyl)dibenzoic acids

5.5.5.1 m,m'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid

2,5-Di-(m-toluoyl)-1,3,4-oxadiazole and an azeotropic mixture of pyridine-water (250 ml)(cf. p. 111) was heated with stirring to 70° in a water bath. Potassium permanganate (50.0 g) was added in small portions. The mixture was heated under reflux for 2 h. The solvent was evaporated under vacuum and the solid so obtained extracted with water (500 ml). The water extract was acidified with hydrochloric acid (2M) and the precipitate obtained filtered off, washed with water (as explained in section 5.5.1.1) and dried. Yield 9.9 g (80%); m.p. 362 ± 2° C (from N-methylpyrrolid-2-one/water; lit.[22] 368-371°); ν_{max}(cm^{-1}) (oxadiazole) 970, (C=O) 1680. (Found: C, 62.2; H, 3.4; N, 9.0. Calc. for $C_{16}H_{10}N_2O_5$: C, 61.9; H, 3.25; N, 9.0%).

5.5.5.2 p,p'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid,

m.p. 425 ± 2°C (lit.[103] 450°); V_{max}(cm^{-1}) (oxadiazole) 970, (C=O) 1690, was similarly obtained using potassium permanganate (40.0 g) in 87% yield. [Found (crude product): C, 61.4; H, 3.4; N, 8.9. Calc. for $C_{16}H_{10}N_2O_5$: C, 61.9; H, 3.25; N, 9.0%].

5.5.5.3 p,m'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid,

m.p. 352 ± 2°C; ν_{max}(cm^{-1}) (oxadiazole) 970, (C=O) 1680, was

similarly prepared using potassium permanganate (45.0 g) in 94% yield. [Found (crude product): C, 61.8; H, 3.55; N, 9.0. $C_{16}H_{10}N_2O_5$ requires C, 61.9; H, 3.25; N, 9.0%).

5.5.6 (1,3,4-Thiadiazole-2,5-diyl)dibenzoic acid

5.5.6.1 m,m'-(1,3,4-Thiadiazole-2,5-diyl)dibenzoic acid,

m.p. 362 ± 2°C; $\nu_{max}(cm^{-1})$ (thiadiazole) 990, (C=O) 1665, was similarly prepared in 78% yield. [Found (crude product): C, 59.5; H, 3.3; N, 8.5. $C_{16}H_{10}N_2O_4S$ requires C, 58.9; H, 3.1; N, 8.6%].

5.5.6.2 p,p'-(1,3,4-Thiadiazole-2,5-diyl)dibenzoic acid,

m.p. 450 ± 2°C; $\nu_{max}(cm^{-1})$ (thiadiazole) 990, (C=O) 1680, was similarly obtained in 92% yield. [Found (crude product): C, 58.4; H, 3.3; N, 8.5. $C_{16}H_{10}N_2O_4S$ requires c, 58.9; H, 3.1; N, 8.6%).

5.5.6.3 p,m'-(1,3,4-Thiadiazole-2,5-diyl)dibenzoic acid,

m.p. 402 ± 2°C; $\nu_{max}(cm^{-1})$ (thiadiazole) 990, (C=O) 1670, was similarly obtained in 89% yield. [Found (crude product): C, 58.1; H, 3.6; N, 8.9. $C_{16}H_{10}N_2O_4S$ requires C, 58.9; H, 3.1; N,8.6%).

5.5.7 Diethyl (1,3,4-oxadiazole-2,5-diyl)dibenzoates

5.5.7.1 Diethyl m,m'-(1,3,4-oxadiazole-2,5-diyl)dibenzoate

m,m'-(1,3,4-Oxadiazole-2,5-diyl)dibenzoic acid (10.0 g) and phosphorus pentachloride (13.5 g) were heated in a Bunsen flame till melted (5-10 minutes) and the mixture heated under reflux for 1 h. Petroleum (50 ml) was added and the mixture refluxed for another hour and then filtered hot. The solid left on filtration was heated under reflux with ethanol (300 ml) for 2 h, and refiltered; the filtrate was concentrated under vacuum to one-sixth of the volume and this on cooling gave crystals of ester. Recrystallised from ethanol, it had a m.p. 122-124°C (lit.[22] 133-134°); Yield 2.4 g (20%); $\nu_{max}(cm^{-1})$ (oxadiazole) 970, (C=O) 1730. (found: C, 65.25; H, 4.8; N, 7.9. Calc. for $C_{20}H_{18}N_2O_5$: C, 65.6; H, 4.95; N, 7.6%).

5.5.7.2 Diethyl p,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoate,

m.p. 216-218°C (from ethanol; lit.[17] 215°); $\nu_{max}(cm^{-1})$ (oxadiazole) 970, (C=O) 1725, was similarly prepared in 37% yield. (Found: C, 66.0; H, 5.0; N, 7.65. Calc. for $C_{20}H_{18}N_2O_5$: C, 65.6; H, 4.95; N, 7.6%).

5.5.7.3 Diethyl m,p'-(1,3,4-oxadiazole-2,5-diyl)dibenzoate,

m.p. 148-150°C (from ethanol); $\nu_{max}(cm^{-1})$ (oxadiazole) 975, (C=O)

1720, 1730, was similarly prepared in 37% yield. (Found: C, 66.0; H, 5.0; N,7.65. $C_{20}H_{18}N_2O_5$ requires C, 65.6; H, 4.95; N, 7.6%).

5.5.8 Diethyl (1,3,4-thiadiazole-2,5-diyl)dibenzoate

5.5.8.1 Diethyl m,m'-(1,3,4-thiadiazole-2,5-diyl)dibenzoate,

m.p. 125-127°C (from ethanol); $\nu_{max}(cm^{-1})$ (thiadiazole) 990, (C=O) 1710, was similarly prepared in 38% yield. (Found: C, 63.2; H, 4.8; N, 7.45. $C_{20}H_{18}N_2O_4S$ requires C, 62.8; H, 4.7; N, 7.3%).

5.5.8.2 Diethyl p,p'-(1,3,4-thiadiazole-2,5-diyl)dibenzoate,

m.p. 266-268°C (from ethanol); $\nu_{max}(cm^{-1})$ (thiadiazole) 990, (C=O) 1710, was similarly prepared in 21% yield. (Found: C,62.8; H, 4.7; N, 7.3. $C_{20}H_{18}N_2O_4S$ requires C, 62.8; H, 4.7; N, 7.3%).

5.5.8.3 Diethyl m,p'-(1,3,4-thiadiazole-2,5-diyl)dibenzoate,

m.p. 120-122°C (from ethanol); $\nu_{max}(cm^{-1})$ (thiadiazole) 980, (C=O) 1710, was similarly prepared in 60% yield. (Found: C, 62.8; H, 4.6; N, 7.4. $C_{20}H_{18}N_2O_4S$ requires C, 62.8; H, 4.7; N, 7.3%).

5.6 Nitration of 2,5-diaryl-1,3,4-thiadiazole

5.6.1 With nitric acid

5.6.1.1 2,5-Diphenyl-1,3,4-thiadiazole (45)

Nitric acid (30 ml, d 1.5) was cooled to 0°C by using ice/sodium chloride mixture. With stirring and cooling 2,5-diphenyl-1,3,4-thiadiazole (45) (1.0 g; 0.0042 mol) was added slowly. Stirring was continued for 4 h. Ice-cold water was added to this mixture keeping the temperature below 20°C. The precipitate formed was filtered off, washed with sodium bicarbonate and then with water till neutral, and dried. Yield 1.34 g (97% assuming dinitration); m.p. 182-188°C.

5.6.1.2 2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole(52)

2-Phenyl-5-(o-nitrophenyl)1,3,4-thiadiazole (0.5 g) was similarly nitrated; yield 0.54 g.

5.6.1.3 2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole(53)

2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.56 g.

5.6.1.4 2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole(54)

2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.53 g.

5.6.2 With nitric acid in sulphuric acid

5.6.2.1 2,5-Diphenyl-1,3,4-thiadiazole(45)

2,5-Diphenyl-5-thiadiazole (1.1 g; 0.0046 mol) was dissolved in sulphuric acid (3 ml, d 1.84) with stirring and external cooling. Nitric acid (1 ml, d 1.5) was added at 0°C. Stirring with external cooling was continued for 3 h. Ice-cold water (100 ml) was added while keeping the temperature below 20°C. The precipitate formed was filtered off, washed with sodium bicarbonate and then with water till neutral. Yield 1.45 g.

5.6.2.2 2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole(52)

2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated. Yield 0.53 g.

5.6.2.3 2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole(53)

2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.56 g.

5.6.2.4 2-Phenyl-5-(p-nitrophenyl)1,3,4-thiadiazole(54)

2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated. Yield 0.55 g.

5.6.3 With nitronium tetrafluoroborate

5.6.3.1 2,5-Diphenyl-1,3,4-thiadiazole(45)

2,5-Diphenyl-1,3,4-thiadiazole (1.08 g; 0.0045 mol) was added slowly to a stirred suspension of nitronium tetrafluoroborate (3.0 g; 0.025 mol) in dry redistilled sulpholane (10 ml) at 30°C. Stirring was continued at 100°C for 2 h. The mixture was poured into ice-water, and filtered. The solid product was washed with sodium bicarbonate and then with water till neutral. Yield 1.4 g.

5.6.3.2 2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole(52)

2-Phenyl-5-(o-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.53 g.

5.6.3.3 2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole(53)

2-Phenyl-5-(m-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.56 g.

5.6.3.4 2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole(54)

2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole (0.5 g) was similarly nitrated; Yield 0.57 g.

5.7 Bromination of 2,5-diaryl-1,3,4-oxadiazoles using bromine and potassium bromate

5.7.1 2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole(35) with oxadiazole:bromine:potassium bromate = 1:1:2

2-Phenyl-5-(p-nitrophenyl)-1,3,4-thiadiazole (1.35 g; 0.005 mol) was added with stirring to a solution of bromine (0.8 g; 0.005 mol), concentrated sulphuric acid (30 ml) and acetic acid (50 ml). The temperature of the mixture was raised and maintained at 25°C and a solution of potassium bromate [0.84 g in water (10 ml)] was added dropwise over a period of 15 minutes. Stirring of the mixture was continued for 1 h, at the end of which another portion of potassium bromate solution [0.84 g in water (10 ml)] was added dropwise over 15 minutes. Stirring was continued for another hour, the mixture was then heated on a water bath (10-15 minutes), cooled and poured into ice-water and filtered. The solid so obtained was washed with water and dried. Yield 1.08 g.

5.7.2 2-Phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole(35)
with oxadiazole:bromine:potassium bromate = 2:1:2

2-Phenyl-5-(p-nitrophenyl)-1,3,4-oxadiazole (1.35 g) was similarly brominated using bromine (0.2 g) and potassium bromate (0.46 g) ; Yield 1.01 g.

5.7.3 2-(o-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(61)
with oxadiazole:bromine:potassium bromate = 34:20:44

2-(o-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole (0.67 g) was similarly brominated using bromine (0.2 g) and potassium bromate (0.46 g) ; Yield 0.49 g.

5.7.4 2-(m-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(62)
with oxadiazole:bromine:potassium bromate = 34:20:44

2-(m-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole (0.67 g) was similarly brominated using bromine (0.2 g) and potassium bromate (0.46 g) ; Yield 0.56 g.

5.7.4 2-(p-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole(63)
with oxadiazole:bromine:potassium bromate = 34:20:44

2-(p-Bromophenyl)-5-(p-nitrophenyl)-1,3,4-oxadiazole (0.67 g) was similarly brominated using bromine (0.2 g) and potassium bromate (0.46 g) ; Yield 0.5 g.

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Synthesis of (1,3,4-Oxadiazole-2,5-diyl)dibenzoic Acids and their Thiadiazole Analogues

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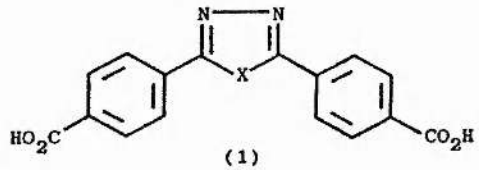
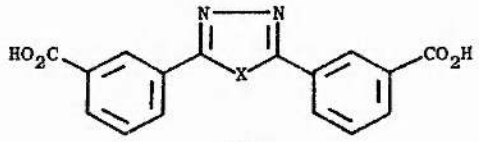
We report that the title compounds are best prepared by oxidation of the corresponding 2,5-ditolyl-1,3,4-oxadiazole or -thiadiazole, and are most easily characterised by the ^{13}C n.m.r. spectra of their dipotassium salts.

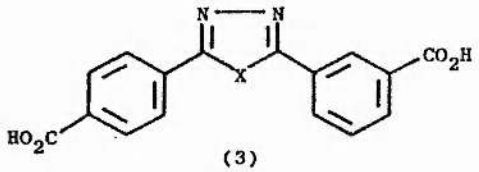
Symmetrical dicarboxylic acids of the type (1) or (2) and their simple derivatives have been used in the past as starting materials for several polymerisation studies, and some of their esters have also been used as polymer additives.



(1)



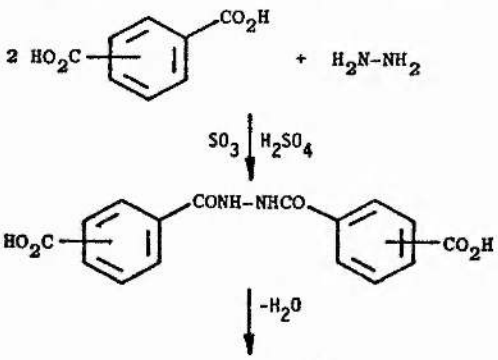
(2)



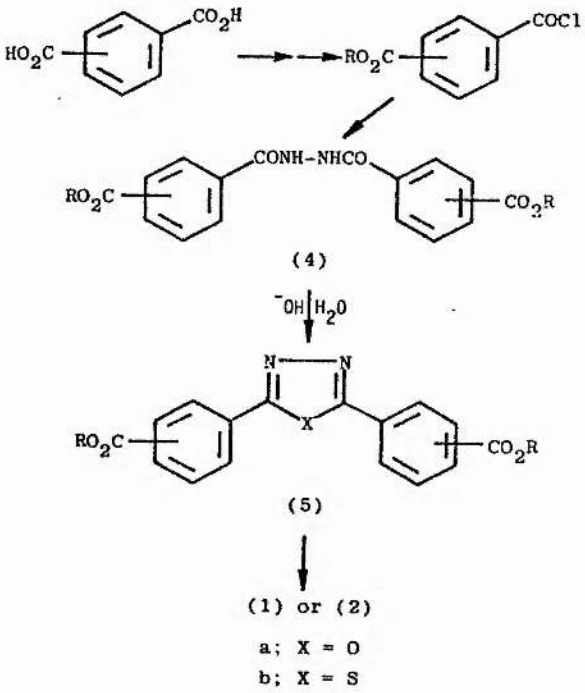
(3)

a; X = O
b; X = S

The two most commonly used routes to (1a) and (2a), both of which are patented methods, proved in our experience to be totally unsatisfactory. Direct reaction of terephthalic or isophthalic acid with hydrazine sulphate in oleum (Scheme 1)[14,17] gave the required acids (1a) and (2a) as very minor components of complex mixtures which were difficult to separate; the more circuitous route involving a suitably protected terephthaloyl or isophthaloyl monochloride and hydrazine (Scheme 2)[6,9,10,13,15] gave mixtures from which the required heterocyclic esters (5) were obtained in only low yield.



Scheme 1



Scheme 2

The simplest route to these dicarboxylic acids involves oxidation of the appropriate 2,5-ditolyl-1,3,4-oxadiazole or -thiadiazole with potassium permanganate in aqueous pyridine (Scheme 3), an adaptation of a Russian procedure[16] for the preparation of (1a). The method is equally applicable to the symmetrical [(1) and (2)] and unsymmetrical (3) isomers, and to oxadiazoles (series a) and thiadiazoles (series b).

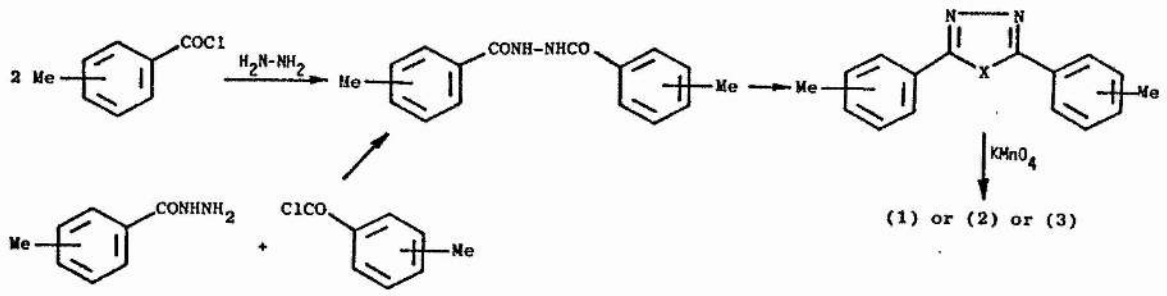
Except in the case of (2a), the acids thus obtained are almost analytically pure without recrystallisation. This is of particular importance since the acids are insufficiently soluble in any of the common solvents to permit easy recrystallisation. The acids are best characterised by the ^{13}C n.m.r. spectra of their dipotassium salts (in D_2O). Complete assignment of all the resonances is possible by using model compounds and (for the carbocyclic rings) the 'substituent parameters' shown in the Table.

Table Substituent effects on ^{13}C n.m.r. shifts[a]

Substituent	*ipso*	*ortho*	*meta*	*para*
CO_2^-	+9.2	+1.5	+1.2	+3.7
1,3,4-Oxadiazole	−8.0	−3.2	−0.4	+2.5
1,3,4-Thiadiazole	−1.9	−2.3	−0.3	+1.8

[a]Expressed in ppm relative to δ_C = 128.5 for benzene.

*To receive any correspondence.



Scheme 3

References: 24

Techniques used: Differential thermal analysis; ^{13}C n.m.r. spectroscopy

Paper: E/223/83 Received: 1st December 1983

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